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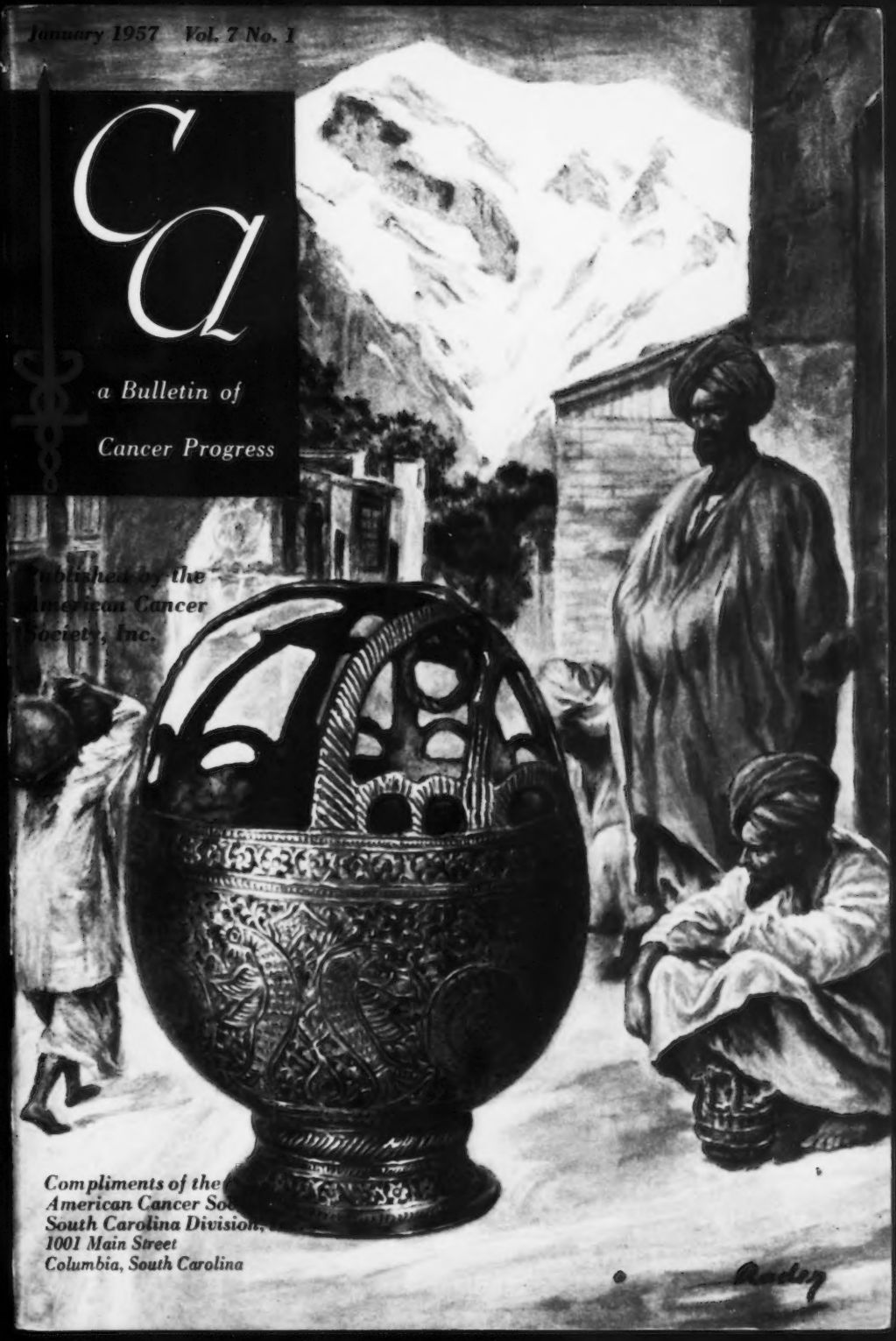

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American Cancer Soc
South Carolina Division,
1001 Main Street
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puncturing the spontaneous

Evidence is accumulating that "spontaneous" cancers are actually induced. Much of this evidence is based on experimental and epidemiological observations.

Nature long since has set up throughout the world long-term experimental programs hardly less valuable in the conquest of cancer than the short-term, man-made laboratory and clinical investigations. Full utilization of these natural phenomena would contribute much to the knowledge of the etiology of cancer.

The few isolated cancer registries in countries with well-developed public-health services point the way to what could be learned over a long period from universal reporting of all cancer cases. Only a beginning has been made in recording, correlating, and analyzing the facts now available. Much remains to be done in studying the incidence, types, and sites of cancer in different racial, geographical, economic, social, cultural, environmental, and occupational groups.

Among the cancers now known to be caused by customs peculiar to a particular geographical section are the chutta, dhoti, and khaini cancers in India, betel-nut cancer in Siam, kangri cancer in Kashmir, kang cancer in China, chimney-sweeps' and mule-spinners' cancers in England, and radium-painters' osteosarcoma in the United States.

Other etiological factors for many kinds of cancer are being discovered in the customs, environments, and occupations of various human groups—smoking, air pollution, radiation, and carcinogenic substances, such as aniline dyes, arsenic and chromium compounds.

Fortunately, many cancers of environmental and occupational origin are preventable by avoidance of the etiological factors. Even "racial" differences now appear to be environmental and controllable rather than genetical and inevitable.

Full exploitation of these promising areas of environmental and occupational research will reveal more and more provocative carcinogenic factors. Possibly most cancers are induced rather than genuinely spontaneous. In fact, the more we learn about everything, the less use there is for "spontaneous," for all effects have their causes even though we cannot identify them.

Cover—

Kangri Jar—Kangri cancers of the skin occur on the anterior abdominal wall or on the thighs at the point of contact with a small brazier containing live coals worn for warmth in cold weather. The bowl hangs from the neck at the level of the lower abdomen when standing, or between the thighs when sitting. Kangri cancer in Kashmir, described as early as 1879 by Maxwell, is but one of the many cancers caused by customs peculiar to various population groups.

NEWSLETTER

JANUARY, 1957

Dr. David A. Wood, University of California Professor of Pathology and the new president of the American Cancer Society, at the close of the Society's annual meeting in New York, Oct. 29-Nov. 2, 1956 emphasized the need for freedom in research. He said: "With the increasing availability of funds for research and the potential monstrosity of bigness, there is a temptation to regulate unduly, to direct inordinately and to lose sight of the individual imaginative investigator as the fountainhead of new ideas, bold concepts and energetic action.

"Great restraint must be exercised in formulating regulations, not only by philanthropic organizations, governmental agencies and academic institutions but also by individuals who would direct research programs. Their responsibility to the public is most grave, and especially so when it comes to cancer.

"Conventional thinking alone will not sustain progress in research. We need new and bold ideas; we need unfettered minds.

"The American Cancer Society is prepared to invest $8,000,000 next year in research; and it will give top priority in its grants to qualified scientists with new ideas and the ability to test them under exacting scientific standards.

"The Society will do its best to guarantee scientists' rights to independence in their investigations and to encourage radical new approaches through fundamental science. Its grants have carried great prestige, and they will continue to do so."

He mentioned as a critical bottleneck in cancer and other research the difficulty of luring talent into science -- "high pay outside and low pay within universities and research institutions" -- and he predicted that the situation would remain acute until it is met realistically. "The Society," he said, "is attacking this problem under a new program to help institutions recruit and retain personnel."

He asserted that "the spirit of defeatism which tra-

ditionally enshrouded the cancer problem and deterred investigators from entering the field has been dissipating rapidly during the last decade." As symbols of progress he cited the present hopeful attitude of both science and the public toward eventual control of cancer, the fact that several chemicals now cure specific transplanted tumors in animals, the growing list of palliatives for human patients, the availability of isotopes and dozens of new laboratory devices for metabolic studies and the increased enlistment of scientists in cancer's basic fields of investigation.

Hormones -- Basic. One day of the scientific sessions was given over to basic work on hormones and one day to clinical observations.

Villee (Harvard) gave substantial evidence to indicate that estradiol acts by binding tightly with a DPN-linked isocitric dehydrogenase and thus converts this enzyme from an inactive to an active state. This apparently starts up the synthetic machinery of cells dependent upon estrogens for growth. Villee isolated the enzyme from nonparticulate fractions of placenta and measured estrogen effect by enzymatic utilization of citrate, production of a ketoglutarate or reduction of DPN. This simple, rapid and reliable process not only offers a means of measuring estrogen activity but lays the groundwork for a possible pregnancy test and suggests new targets for chemotherapy in estrogen-dependent tumors.

Gardner (Yale) reported that estrogen administration has induced tumors of at least 13 sites, including breast, uterine cervix, vagina, testes, pituitary, kidney, bladder, and lymphoid tissue of experimental animals. He pointed out that some strains and species are susceptible to certain cancers induced endocrinologically while others are not. The secret of susceptibility or resistance, he said, seems to lie in the response of the target organs themselves. He also reported that testosterone and its esters, when given in large amounts beginning early in life, prevent some but not other estrogen-induced cancers. The male hormone prevents leukemogenic effects of x-rays and estrogen. In very few instances, he said, estrogen acts directly on tissues to bring about cancer -- notably when an estrogen pellet is implanted in the vagina. He surmised that estrogen may: (1) give rise to carcinogenic metabolic derivatives (not

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Keeping up

Hormonal Influences on Cancer

A review of the development of the hormone treatment of carcinoma of the breast and prostate is presented, and the need for selection of cases that are hormone dependent is emphasized. Two methods are described by which such hormone dependency may be evaluated: the sex-hormone stimulation test, in which results are evaluated by observation of increased urinary-calcium levels and subjective symptoms; and the cortisone-inhibition test, in which the result is assessed by the decrease in urinary-calcium excretion and improvement in subjective symptoms. The rationale of the modern palliative treatment of advanced carcinoma of the mammary and prostate glands by endocrine therapy is based on the alteration of the hormonal environment of the cancer cell. It is postulated that, by administration of the appropriate hormone —whether it is estrogen, androgen, or cortisone—or by its removal by castration, adrenalectomy, or hypophysectomy, the tumor-host relation is altered in favor of the host, and an increase in resistance to the growth of the tumor cells results. In several series of cases in which carcinomas of the breast and prostate were treated by bilateral adrenalectomy a good objective response has been reported in 30 to 40 per cent of patients, while the remainder were unaffected or made worse by the operation. Patients who responded apparently had hormone-dependent tumors and had usually derived benefit from preceding gonadectomy. Persons with autonomous growths are not benefited by such procedures and should be spared the operative mortality and attendant morbidity. The selection of tumors that will respond to gonadectomy or bilateral adrenalectomy has become of critical importance, therefore, because it is on such patients that operation must be advised. Hitherto, attempts at selection have been made as follows: study of the results achieved by previous hormonal alteration, as in patients who have obtained a good clinical remission with gonadectomy and hence will probably benefit from adrenalectomy; study of the histological type of the primary tumor, as in carcinoma of the breast, in which Huggins and Scott believe that the adenocarcinomas will respond to adrenalectomy because these cells are more highly differentiated and therefore more readily controlled by circulating estrogens. Other workers do not regard the histological type of the primary tumor as bearing any relation to the result achieved. In patients with osseous metastases the study of calcium excretion in the urine may be used to select patients for operation. To evaluate patients for gonadectomy, a sex-hormone test is used. The patient's diet is planned to contain a maximum calcium intake of 200 mg., and the daily twenty-four-hour urinary-calcium excretion is determined. A healthy person on this intake will excrete about 50 to 100 mg. of calcium a day. Calcium excretion rises with osteolysis. When 1 gm. of bone is destroyed by neoplastic tissue, about 100 mg. of calcium is liberated and excreted in the urine. After a control period of five to seven days, a provocative dose of hormone is administered. With prostatic cancer, 100 mg. of testosterone propionate intramuscularly is given daily for three consecutive days. With carcinoma of the breast, 5 to 10 mg. of stilbestrol is admin-

with Cancer

istered over a similar period. A positive response to the test, which is indicative of hormone dependency of the tumor, is determined by (1) mobilization of calcium from the skeleton, which causes hypercalcinuria and occasionally hypercalcemia; and (2) a systemic reaction, with malaise, increased bone pain, pyrexia, and lethargy. The rapidity of onset and the extent and duration of hypercalcinuria apparently depend on both the degree of hormone dependency of the tumor and the extent and size of the osseous metastases. With only a few bony metastases, urinary-calcium excretion will be increased relatively little. If soft-tissue metastases predominate over osseous lesions, the systemic reaction will be more prominent than the calcium mobilization. When the response is positive, the urinary calcium usually rises within two to three days after stimulation and often persists for several weeks. The systemic reaction may be severe enough to require gonadectomy or adrenalectomy. When a patient has an exacerbation of disease subsequent to gonadectomy, the cortisone-inhibition test may be used to predict the value of bilateral adrenalectomy. After administration of cortisone, a positive response is indicated by a decrease in urinary-calcium excretion and subjective improvement.

Emerson, K., Jr., and Jessiman, A. G.: Hormonal influences on the growth and progression of cancer; tests for hormone dependency in mammary and prostatic cancer. New England J. Med. 254: 252-258, Feb. 9, 1956.

Radiotherapy of Bronchial Carcinoma

A group of 207 patients with bronchial carcinoma without extrathoracic metastases and treated by radiotherapy is compared with a group of 248 who received no treatment likely to prolong life. An estimated tumor dose of 1000 to 3900 r was used in 114 patients and of 4000 r or more in ninety-three. Of the 248 control patients, thirty-three died within two months and were excluded from the comparison group, leaving 215 to compare with the ninety-three patients who received 4000 r or more. The patterns of survival, judged by the proportions living for successive six-month periods, were not greatly different in the treated and untreated patients. There appeared to be no conclusive evidence that radiotherapy prolongs life or that large doses have greater effect on survival than small doses. It is unlikely that radiotherapy caused an increase of as much as 10 per cent in those surviving one year after diagnosis or of 5 per cent in those surviving for two years.

Bignall, J. R.: Bronchial carcinoma; effect of radiotherapy on survival. Lancet 1: 876-879, June 9, 1956.

Cancer of the Breast—Diagnosis

Excisional or incisional biopsy of all breast lumps, with examination of sections made on the freezing microtome, is the method by which breast cancer can be diagnosed most quickly and accurately. Diagnosis of breast cancer is easy when it has progressed to the stage of skin edema, nipple changes, and axillary node enlargement. Patients are advised to report to their physicians the slightest symptoms referable to their breasts, but at least 10 per cent of those reporting are given erroneous advice and inappropriate treatment by the first physician they consult. Perhaps one half of the breast cancers that appear to be localized to the

breast already have impalpable axillary metastases. Even when the tumor was only bean or pea size at the time of operation, two fifths of the patients followed for periods longer than five years eventually died of cancer. Such evidence of biological variability of breast cancer indicates that early diagnosis cannot result in complete control of the disease. Yet, since we cannot predict which patient will and which will not benefit, the plea for earlier diagnosis is fully justified. The patient should be told at the first examination that it is impossible to diagnose a lump as cancer or benign without microscopic examination. An accidentally discovered lump in the breast is the presenting complaint in 90 per cent of instances. Axillary metastases are sometimes palpable before the primary lesion in the breast. Other diagnostic methods—profile radiography, transillumination, cytology, roentgenography, infrared phlebography, and blood and serum tests—cannot approach the accuracy of microscopic examination. There is almost universal agreement now that the treatment of choice for breast cancer thought to be limited to the breast, or to the breast and the axilla on the same side, is the standard radical mastectomy of Halsted and Willy Meyer and that an operation of lesser extent is justified only as a palliative measure.

River, L., and Silverstein, J.: The diagnosis of carcinoma of the breast. S. Clin. North America 36:35-48, Feb., 1956.

Treatment of Prostatic Cancer

The majority of cancers of the prostate are beyond any hope of cure when first seen. Palliation therapy is designed to make the patient live as long and as comfortably as possible. Orchiectomy alone is the recommended treatment for the patient with signs and symptoms of extension of prostatic cancer but without urinary symptoms. If urinary symptoms with residual urine are present the patient should have transurethral resection in addition to orchiectomy. If there is no evidence of metastases but urinary symptoms are present the patient should have transurethral resection and should be watched carefully for regrowth or extension, when he should be treated with estrogens or by castration. In the case with obvious metastases or with elevated acid phosphatase the preferred treatment is bilateral orchiectomy, with transurethral resection if urinary symptoms are present. Recurrence of symptoms and regrowth of the gland occur in spite of orchiectomy and hormone therapy, and the "time-honored" methods of terminal care—opiates, etc., —must be resorted to. All patients should be told of their disease; the patient has a right to suspect anyone who wishes to relieve him of two of his most prized possessions for a disease which has been falsely described as something very minor. Patients with prostatic cancer live much longer and more comfortably than they did in the past.

Milner, W. A., and Garlick, W. B.: Modern treatment of carcinoma of the prostate. New York State J. Med. 56:100-101, Jan. 1, 1956.

Pituitary Irradiation in Breast Cancer

Fifty patients with advanced cancer of the breast were treated by implantation of unscreened grains of radioactive gold into the anterior part of the pituitary gland by way of the nose and sphenoidal sinus. Accurate localization of the sella turcica was obtained by means of an image intensifier working in two planes. Unlike other workers the author relied on smaller and, if necessary, repeated doses of beta-irradiation. Unlike the procedures of adrenalectomy and hypophysectomy this procedure does not add further to the patient's suffering. The author considers adrenalectomy unjustified unless it gives a clear remission of the disease with complete alleviation of pain for at least a year.

With this new procedure in fifty consecutive cases there has been no mortality or complications even though many of the patients were unfit for adrenalectomy. There was no evidence of damage to the optic chiasm. Vision was improved in two cases with choroidal metastases. No case of basal meningitis or of cerebrospinal rhinorrhea occurred. After further

careful assessment and follow-up this method of accurate implantation and controlled dosage may prove a safe additional palliative measure in advanced carcinoma of the breast.

Greening, W. P.: Irradiation of pituitary for advanced mammary cancer. Lancet 1:728-729, May 19, 1956.

Treatment of Soft-Tissue Tumors

The best opportunity to cure a patient with a soft-tissue sarcoma is at the time of initial treatment. If a nodule is dismissed as insignificant or excised without histologic examination, the malignant tumor may go undetected. Sarcomas may occur at any age, often during infancy and childhood, and in any part of the body that contains parent tissue. Though the extremities are the most common sites, the neck, chest wall, and retroperitoneal space are not infrequently involved. Malignant soft-tissue tumors probably do not arise from pre-existing fibromas, lipomas, myomas, or other benign lesions. Trauma apparently is not a precipitating factor but rather calls attention to a tumor already present. A limb with a tumor may be more liable to injury. Fibrosarcoma, the most common soft-tissue sarcoma, forms a round or ovoid, firm, homogeneous mass that may appear encapsulated. Degree of fixation varies, and periods of inactivity alternate with those of growth, invasion, and metastases. Liposarcoma, the second most frequent soft-tissue malignant tumor, often occurs in the gluteal and popliteal regions and is the most frequent primary sarcoma in the retroperitoneal space. The lesion is usually firmer, more nodular and fixed, and less easily compressed than the benign lipoma. Rhabdomyosarcoma, the malignant tumor arising in skeletal muscle, is usually deep seated and firm. The tumor may undergo extensive hemorrhagic necrosis, simulating a large hematoma. The malignant neurilemoma originates in a nerve sheath, generally along a recognized peripheral stream to the lungs; synovial sarcomas may spread through lymphatics and necessitate lymph-node dissection. Radiotherapy is the best treatment for Kaposi's sarcoma. Many undifferentiated liposarcomas are radiosensitive, and, if the resected tumor was recurrent, postoperative irradiation is advisable. Inoperable primary retroperitoneal sarcomas are irradiated. Periodic examinations including careful search for local recurrence and frequent chest roentgenograms must be made for the duration of the patient's life. Regardless of individual characteristics, the most important feature of all of the soft-tissue sarcomas is their great tendency to recur locally. The physician or surgeon should carefully attempt to catalog or identify all soft-tissue nodules when the patient is first seen. All nodules that are firm, fixed, or deep seated; those causing pain or discomfort; and those with a history of recent growth should be excised and examined histologically.

Burdick, D.: Treatment of soft tissue tumors. New York State J. Med. 56:722-725, March 1, 1956.

Cervical Carcinoma in Situ

Clinical data concerning 275 patients with Stage-0 cancer of the cervix seen at Duke University from January, 1952 to June 30, 1955 are scrutinized from the standpoints of early diagnosis, results of "conservative" and "definitive" treatment, and relation to pregnancy. All patients in gynecological and obstetrical departments, regardless of age, parity, economic status, or race should be systematically searched for cancer. Vaginal hysterectomy with removal of an adequate vaginal cuff and with conservation of the ovaries in the younger age groups is the operation of choice. Eleven patients with Stage-0 cancer became pregnant after the diagnosis was established. Three of these had had definitive operative treatment, and the other eight are being followed. No patient being followed without definitive treatment has developed invasive squamous-cell cancer of the cervix. All patients with Stage-0 cancer of the cervix or of the cervical stump should be followed with adequate diagnostic techniques whether they have had conservative or definitive treatment. Meigs (in discussion) says that histologic slides of 20 different cervi-

cal lesions were examined by 24 pathologists. Their diagnoses showed absolutely no consistency. Pathologists in the same department, chief and assistant, disagreed. This may well explain the variations in incidence of carcinoma in situ in different clinics. All patients after treatment of any cancer of the cervix should be followed with vaginal smears to pick up recurrences after treatment of carcinoma in situ as well as after surgery or radiation for invasive cancer. It is very reprehensible to allow patients to go without treatment after a diagnosis of carcinoma in situ has been made.

Carter, B.; Cuyler, W. K.; Kaufmann, L. A.; Thomas, W. L.; Creadnick, R. N.; Parker, R. T.; Peete, C. H., Jr., and Cherny, W. B.: Clinical problems in Stage 0 (intraepithelial) cancer of the cervix. Am. J. Obst. & Gynec. 71:634-650; disc. 650-652, March, 1956.

Radiation vs. Surgery in Uterine Cancer

A difficulty in securing comparability of different statistics concerning results of treatment of cancer of the uterus is that patients reported from different centers are not of equal clinical quality. The various therapeutic procedures cannot be reliably evaluated from such selected material. In order to compare different therapeutic results, an accepted clinical staging prior to any treatment is essential. Although international agreement has been reached on definitions of the various stages of cervical cancer, there remains considerable difference of opinion concerning interpretation of these definitions. Of seventy-four patients with carcinoma in situ at the Radiumhemmet, twenty-three have developed invasive carcinoma. Radical operation or irradiation should not be routinely performed in carcinoma in situ. Many younger women may have been harmed more by the treatment than is compensated for by the protection. Although efficient surgical treatment gives relatively high cure rates and low mortality rates in selected cases, bladder, rectovaginal, and ureterovaginal fistulae occur in roughly 9 to 14 per cent of the cases operated upon at centers particularly interested in surgical therapy. At the Radiumhemmet, after careful cystoscopic, urographic, and phlebographic examinations, fractionated intracavitary radium treatment and roentgen-ray therapy to the parametrium and the pelvic wall are given. In selected cases of suspicious lymph-node metastases radioactive colloidal gold is injected into the parametrium. Additional telecobalt treatment is applied in selected cases. Radiation therapy and radical surgery can be compared only in a single institution, as in the series reported by Twombly and Taylor who obtained the best results from irradiation alone. Late recurrences are said by the surgeons to be less frequent after surgery than after irradiation, but ten-year–cure rates do not support this. However, surgery has a great contribution to make in those cases that fail to respond to radiotherapy and in those that recur. The question to be answered is not one of surgery versus radiotherapy, but one of selection of the treatment of choice for the individual patient.

Kottmeier, H. L.: The place of radiation therapy and of surgery in the treatment of uterine cancer. J. Obst. & Gynaec. Brit. Emp. 62:737-751; disc. 751-773, Oct., 1955.

Recurrent Carcinoma of the Colon

Carcinoma recurred at the anastomotic site in 21 of 140 patients after primary resection of the colon. The usual site of the primary tumor was the sigmoid colon. Neither the time interval between operation and recurrence, the margin between the lesion and the distal line of resection, nor the length of bowel removed was correlated with recurrence. Implantation of exfoliated tumor cells upon the suture line may sometimes be responsible for recurrence. However, incidence of recurrence is significantly greater in the left than in the right side of the colon, a circumstance not explicable by intraluminal dissemination of exfoliated cells. Since neoplastic growth often penetrates the entire bowel wall, resultant obstruction to lymphatic flow may sometimes cause retrograde tumor extension through the pericolic lymphatics. Colonic papillomas which eventually become malignant may account for recurrence in many instances. Distal as

well as proximal extension of the line of transection is important. In resection of the left colon, the anastomosis should be placed within reach of the sigmoidoscope; left hemicolectomy may be advisable for left colon growths. Removal of all satellite papillomas should further reduce incidence of recurrence; re-resection when recurrent growth is detected may increase survival. Distal extension of the line of transection, careful examination of the entire colon at the time of operation, and repeated investigations for papillomas or other neoplasms postoperatively are important means for reducing anastomotic recurrence of colonic carcinoma.

Beal, J. M., and Cornell, G. N.: A study of the problem of recurrence of carcinoma at the anastomotic site following resection of the colon for carcinoma. Ann. Surg. 143:1-7, Jan., 1956.

Radioactive Gold in Effusions

At the Toronto General Hospital, ninety-nine patients with pleural and peritoneal effusions complicating malignant neoplasms were treated by instillation of radioactive colloidal gold. In forty-three patients with breast cancer, forty-four chest and six abdominal instillations resulted in improvement in twenty-two (44 per cent), all following chest instillations. In eighteen cases of carcinoma of the ovary, seven chest and fourteen abdominal instillations resulted in improvement in seven cases (30 per cent). In sixteen patients with secondary carcinoma of unknown primary origin, nine chest and eleven abdominal instillations resulted in improvement in ten cases (50 per cent). Results in lymphoma and in cervical carcinoma were disappointing. The over-all result of eighty chest and thirty-six abdominal instillations in the ninety-nine patients was improvement in forty patients. The procedure is valueless in nonmalignant effusions, such as that from cardiac failure. As time is required for results the method should not be used in very ill or cachectic patients. Unless there is a reasonable hope of survival for several months the patient should not be subjected to the needless expense and trauma. Life has not been prolonged but the instillations relieve the symptoms of rapidly accumulating fluid. There was no improvement in patients with abdominal masses. They are better treated by external radiation. Good results are sometimes obtained in unexpected cases. Use of the method should be limited to those cases in which tapping is repeatedly followed by prompt accumulation of fluid. A second instillation of gold should be given only if the first clearly suppressed fluid formation for many months.

Millar, O., and MacDonald, J. C. F.: Radioactive gold in malignant effusions. Canad. M. A. J. 74:783-788, May 15, 1956.

Fatal Cervical Carcinoma

With a view to improving the management of cancer of the cervix, a study was made of the autopsy material of fifty-eight patients who died of this disease at Milwaukee County Hospital during 1942 and 1943. It was found that conclusions concerning the causes of death based solely on clinical charts are inaccurate. Uremia was three times as common as any other cause of death. Uremia together with pyelonephritis ("renal causes") accounted for 39.6 per cent of the deaths. Among the other causes of death were pulmonary metastasis, peritonitis, pelvic abscess, intestinal obstruction, intestinal perforation, septicemia, cachexia, anemia, hemorrhage, and unrelated causes. The character of the death is the same whether the patient receives adequate, partial, or no treatment. Three patients had no residual carcinoma, and one had an early lesion first discovered at autopsy. Of the remaining fifty-four patients, twenty-four (44.4 per cent) died with the carcinoma limited to the pelvis. Twelve of these would have been poor surgical risks because of age, heart disease, severe anemia, cachexia, etc.; but the other twelve might better have been considered for radical surgery. Radiation therapy per se caused no deaths.

Bartzen, P. J.; Hovis, W. F., Jr., and Albrecht, D. J.: Fatal carcinoma of the cervix; a study of 58 autopsies. Am. J. Obst. & Gynec. 71:143-146, Jan., 1956.

a glance . . .

one-minute abstracts of the current literature on cancer . . .

Irradiation as a Cause of Cancer

Many recent reports stress the occurrence of malignant lesions in children and adolescents who have been irradiated in infancy or early childhood for thymic enlargement, pertussis, cervical adenitis, enlarged tonsils, adenoid tissue, or sinusitis. The incidence of carcinoma of the thyroid gland in children and adolescents is increasing. The high incidence of prior irradiation in these cases strongly suggests an association between the thyroid cancer and the irradiation, but the evidence is not yet conclusive. The apparent increase in incidence of thyroid cancer and leukemia associated with increased irradiation of the head, neck, and chest suggests the possibility that infants have been treated unnecessarily for thymic enlargement when it was asymptomatic or when it did not actually exist. Enlarged thymus is frequently diagnosed from films showing merely a widened mediastinum or a prominent thymus owing to the expiratory phase of the film. A good inspiratory film narrows the mediastinum and makes the enlarged thymus disappear. Most pediatricians and radiologists now believe that the thymus gland seldom, if ever, produces respiratory embarrassment or other symptoms. It is unlikely that the recent increased use of extensive roentgen-ray diagnostic procedures, such as cardiac catheterization and angiocardiography, will lead to an increase in tumors, because the dosages of radiation are usually small and the procedures are not repeated at close intervals. It has been suggested that radiation produces irreversible changes in thyroid cells rendering them more liable to tumor formation when stimulated to undergo hyperplasia by prolonged pituitary thyrotropic stimulation after interference with thyroxine production. Until analysis of many more patients can be made and more definite conclusions can be drawn, ionizing radiations should be used, with but few exceptions, only for malignant tumors.

Dennis, J. M.: Association of irradiation with neoplasia in children and adolescents. [Editorial.] Ann. Int. Med. 44:579-583, March, 1956.

Environmental Causes of Lung Cancer

Several general environmental and specific occupational air pollutants have been incriminated in the causation of lung cancer. The widespread presence of industry-related atmospheric pollutants of recognized carcinogenic properties suggests that the recent alarming rise in lung-cancer frequency, especially among men, may in part be causally related to the local and general development of modern industry and the use of its products. Death rates for this disease have been consistently higher among inhabitants of industrial

cities than among those of rural areas. Male industrial–life-insurance policyholders who are engaged in manufacturing, mining, and transportation and who come from low-income groups have lung-cancer rates 30 to 50 per cent higher than general policyholders who are engaged in office work. Nonferrous metal workers and transportation employees have the highest incidence of lung cancer and farm laborers, the lowest. Male workers exposed to soot from coal tar and oil-burning power plants, to metal fumes and dust, and to arsenicals, gas, asbestos, hydrocarbons, and radioactive ores have higher lung-cancer death rates than men of the same age in the general population. Women in similar occupations have lung-cancer–attack rates comparable to those of men. More closely correlated with the lung-cancer–death rate than with per capita consumption of cigarettes are: the increased production and consumption of coal tar, petroleum products, and carcinogenic metals and minerals or the construction of asphalted roads. If the latent period for lung-cancer development is twenty years, the death rate should have been higher during 1931 to 1944 than the annual progression rates were for deaths in the United States during 1914 to 1930, if cigarette smoking were an important factor in frequency. Variations in the male : female ratio in different population groups are not attributable to fluctuations in the intensity of a single factor such as cigarette smoking but rather to alterations in the type and activity of many environmental carcinogens that affect men and women differently. For occupational reasons, men are more consistently and intensely exposed to cancer-producing atmospheric pollutants than women. Experiments on animals have demonstrated that coal tar, soot, pitch, mineral and petroleum oils, and carbon black are carcinogenic, while the best experimental evidence regarding carcinogenic properties of tobacco tar reveals only slight carcinogenic effects on selected strains of sensitive animals.

Hueper, W. C.: Environmental causes of lung cancer. Pub. Health Rep. 71: 94-98, Jan., 1956.

Cancer and Prenatal Environment

In England a survey is being conducted to determine the possible effect of roentgen-ray examinations of the abdomen during pregnancy in causing malignant tumors in the offspring. Public health departments throughout the country are interviewing the parents of some 1500 children who died of leukemia, and, as control, an equal number of mothers of children who died of other causes. Analysis of approximately one third of the case-material gathered so far makes it apparent that beside the previously known genetic damage to the fetal gonads, diagnostic pelvimetry may occasionally cause leukemia or cancer in the unborn child. Forty-two of the mothers in the leukemia group compared with twenty-four in the control group had had antenatal roentgen-ray examination; and in the other group the number was forty-three compared with a control figure of twenty-one. Editorial comment in this issue of *Lancet* emphasizes the value of this epidemiological approach to such clinical problems. Human epidemiological investigation is a relatively new and extremely powerful means of research which has not yet been fully exploited. The use of field surveys is one of the most profitable methods of inquiry, and one which can provide human data in abundance. This type of investigation merits wholehearted cooperation from all sections of the medical profession and of the community.

Stewart, A.; Webb, J.; Giles, D., and Hewitt, D.: Malignant disease in childhood and diagnostic irradiation in utero. Lancet 2:447, Sept. 1, 1956.

Occupational Tumors

Occupational tumors may be defined as those having abnormally high incidence in certain occupations because of exposure to specific factors related to these occupations. The specifications classifying a tumor as occupational are: (1) it must be a true tumor, not merely granulomatous proliferations like those following exposure to beryllium, (2) statistical data must show its incidence to be higher in

the occupation concerned than in the general population, and (3) contact with one or more cancerigenic substances must exist in the occupation. Since the beginning of the present century there has been a great increase in the number of cancerigenic agents used in industry. Although occupational tumors constitute a small part of the total number of cancers they are of great interest in the general control of cancer. They give the opportunity of studying the mode of action of certain carcinogens and of developing methods of cancer prevention. Among the carcinogenic agents implicated in occupational tumors are: aromatic amines (α- and β-naphthylamine, aniline, benzidine, fuchsin, and auramine), oil-distillation products, radiations (roentgen, gamma, and actinic), compounds of arsenic, chromium, and nickel, asbestos, and isopropyl alcohol. Five to 50 years' exposure may be required for the development of occupational tumors. Preventive action must, therefore, be taken against all occupational exposures to substances known or suspected to be carcinogenic.

Oltramare, M.: Les tumeurs professionelles. [Occupational tumors.] Zeit. f. Unfallmed. u. Berufskr. 48:107-127, June, 1955.

Coal Oils and Cancer

Nine fractions of oil obtained over the entire range of the direct hydrogenation of coal by the Bergius process were tested percutaneously and intramuscularly in mice, rabbits, and rats. Eight of these nine fractions, ranging from pitch to unfinished gasoline, induced carcinomatous or sarcomatous lesions by one or both routes of administration. Carcinogenic potency decreased with the decrease in boiling point of the fractions. Distinct differences in carcinogenicity of the three species tested indicate the necessity for using several species in the screening of chemicals for carcinogenic properties. In the Fischer-Tropsch synthesis carbon monoxide and hydrogen under high pressure and temperature yield hydrocarbons resembling petroleum. Several of these oils were found to be definitely carcinogenic in rats, doubtfully in mice, and not at all in rabbits. Species specificity of these oils paralleled those of the Bergius oils and petroleum derivatives. The effects of the Fischer-Tropsch oils, like those of the Bergius oils, may not be restricted to the tissues in which they are deposited, but may also extend to remote organs.

Hueper, W. C.: Experimental carcinogenic studies on hydrogenated coal oils. I. Bergius oils. Ind. Med. & Surg. 25:51-55, Feb.; II. Fischer-Tropsch oils. 459-462, Oct., 1956.

Demographic and Geographic Incidence of Cancer

The total incidence of cancer is much the same in all countries where life expectancy is comparable but the site incidences vary widely. Stomach cancer, for example, is twice as frequent in Scandinavian countries as in Great Britain. Different socioeconomic groups within the same country differ in regard to cancer of some sites, such as skin and upper alimentary tract, but not of others, e.g., lungs and rectum. The number of known industrial and environmental carcinogens is increasing. The carcinogen 3,4-benzpyrene is found in coal tar, pitch, soot and in atmospheric pollution, particularly of industrial areas. Such a simple change in human habits as from cooking in iron vessels to cooking in vessels of glass may influence the environmental cancer hazards. Cottonseed oil heated in iron vessels is more carcinogenic for the forestomachs of mice than that heated to the same degree in glass vessels. The association of cigarette smoking and lung cancer seems to be established beyond all reasonable doubt.

Peacock, P. R.: Discussion on cancer research: its present trends. Proc. Roy. Soc. Med. 49:664-665, Sept., 1956.

Cancer and Cutting Oils

Six cases of histologically verified squamous-cell carcinoma of the arm or hand and one of papilloma were found among 500 to 800 machine operators over a period of ten years, suggesting a possible relationship between these lesions and long-continued exposure to cutting oils.

The average period of exposure was 21 years. Fractions of these oils boiling between 650° and 800° F. were highly tumorigenic in C3H but not in C57 black mice.

Mastromatteo, E.: Cutting oils and squamous-cell carcinoma. Part I: Incidence in a plant with a report of six cases. Brit. J. Indust. Med. 12:240-243, July, 1955.

Cutting Oils and Skin Cancer

Using standard skin-painting technique, 19 to 61 per cent of tumors were obtained in several strains of mice, after 310 days' exposure, by a soluble industrial cutting fluid—an oil in water emulsion. The oil base was a 50-50 blend of sulphurized and filtered straight-run distillates, uncracked and without additives. The results were reproducible and comparatively constant in repeat tests after an interval of 18 months. Aqueous dilution of the emulsion, 1:4 and 1:8, produced markedly fewer tumors in 365 days' exposure and an increased induction period. With sufficient extension of the skin-painting period, the absolute tumor response was similar.

Gilman, J. P. W., and Vesselinovitch, S. D.: Cutting oils and squamous-cell carcinoma. II. An experimental study of the carcinogenicity of two types of cutting oils. Brit. J. Indust. Med. 12:244-248, July, 1955.

Food Additives as Environmental Carcinogens

The rapidly growing interest in the role of environmental physical and chemical agents has focused attention upon the possible cancer hazards among food additives and contaminants. Many substances added to foods in their processing, merchandizing, and preservation have not been subjected to detailed, long-term investigation for carcinogenicity. During recent years quite a number of chemicals, identical with, or similar to those used in foodstuffs, have been shown to have carcinogenic properties. Epidemiological human evidence shows drinking water, wine, etc., contaminated with arsenicals from industrial sources or from insecticide residues to cause cancer of the skin. Similar carcinogenic effects are known to result from coal tars, petroleum products, and radioactive matter. Synthetic estrogens used to fatten poultry are known to be carcinogenic. Many of the pesticides are tumorigenic. Some synthetic dye stuffs produce cancer in rats and mice. It has been suggested that it might be wise to consider all chemical agents which have elicited cancer in animals as having properties for producing cancer in the human organism. The author suggests: (1) a thorough study of the entire problem; (2) the study of all food additives and contaminants before and after subjection to processes used in food preparation; (3) development of criteria for evaluating the experimental evidence, and (4) dissemination of information concerning the actual and potential cancer hazards of all known food additives and contaminants.

Hueper, W. C.: Potential role of non-nutritive food additives and contaminants as environmental carcinogens. [Special Article.] A.M.A. Arch. Path. 62: 218-249, Sept., 1956.

Lung Cancer from Metallic Oxides

In the 16th century Agricola and Paracelsus described "mountain disease," a lung condition among the Erzgebirge metal-ore miners that was identified two centuries later by Haerting and Hesse as lung cancer. After twenty years' work in the mines, 75 per cent of these miners died of cancer of the lung. Similarly, lung carcinoma was found in half the Schneeberg miners at necropsy. The principal ores in the Schneeberg mines are sulphides and arsenides of nickel and cobalt. On the southern side of Erzgebirge, at Joachimstal there is a high content of pitchblende and radium. Although the bore dust of these mines contained nearly one half of 1 per cent of arsenic, it is probable the radioactivity of the dust produced the tumors. In an English town where the principal industry is the manufacture of arsenical sheep-dip, carcinomas of the lung and skin occur twice as frequently among the workers handling arsenic as among the general population. Cigarette smoke contains 2.5 to 3.5 mg. arsenious oxide per cubic meter and may account

for the world-wide increase in the mortality rate for lung cancer. Chromium trioxide, but not the bichromates or chromic acid, has been shown to produce cancers of the lung and nares after industrial exposure for 10 to 15 years. Control of industrial fumes and dusts is important in preserving the worker's health in the plant and at home. These noxious substances play a bigger part in production of disease than is generally recognized and they will play a still greater part in the future.

Perry, K. M. A.: Pulmonary disease in relation to metallic oxides. Lancet 2:463-469, Sept. 3, 1955.

Environmental Cocarcinogens

In malignant lesions arising in protective epithelia, i.e., the skin, the upper respiratory, upper gastrointestinal, and lower genitourinary tracts, chronic disease, occupation, personal habits, atmospheric pollution and physical environment carry a significant carcinogenic risk. Investigation of these risks is an integral part of fundamental cancer research. Inorganic salts of arsenic are carcinogenic to man but not to animals. Seventy-two occupations involve contact with arsenic. Lung cancer is 16 to 80 times as common among chromium workers as in the general population. Crude tar is used in many occupations. The latent period for industrial cancer varies from 5 to 20 years. An epithelial surface subjected to continuous sub-carcinogenic concentrations of carcinogen is said to be "initiated" and becomes highly "reactive" to local stimulation, as, for example, by the weak carcinogen, croton oil. Even noncarcinogenic irritant chemicals, ultraviolet light, heat below 100°C., and solid carbon dioxide are capable of "promoting" malignant tumors in initiated surfaces. A man whose occupation exposes him to sub-carcinogenic doses of a carcinogen may develop cancer because another carcinogen, at subthreshold dosage, is added to his industrial process, or when he changes his occupation to one in which he is exposed to a dissimilar carcinogen. The multiple lesions of chronic arsenical dermatitis and their progression to carcinoma in situ and infiltrating cancer afford a striking example of increased cellular reactivity of a surface epithelium "initiated" for long periods by sub-carcinogenic doses of a carcinogen.

Hadfield, G.: Co-carcinogenesis. Proc. Roy. Soc. Med. 49:662-664, Sept., 1956.

Asbestos and Cancer

The carcinogenic properties of asbestos are believed by the author to vary with its physical characteristics and its chemical composition. The clinical and experimental evidence concerning asbestos as a carcinogen is not concordant. A case of cancer of the lung, confirmed microscopically, in a woman 49 years of age who had worked for 29 years as a spinner in an asbestos factory, is detailed.

Rombolà, G.: Asbestosi e carcinoma pulmonare in una filatrice di amianto; spunti sui problema oncogeno dell'asbesto. [Asbestosis and pulmonary carcinoma in an asbestos spinner; notes on the carcinogenic properties of asbestos.] Med. d. lavoro 46: 242-250, April, 1955.

Dyes and Bladder Cancer

Rehn in 1895 noted the high incidence of carcinoma of the bladder among men engaged in the manufacture of "aniline" dyes. Since that time the studies of Hueper and other investigators have shown clinically and experimentally that 1- and 2-naphthylamine and benzidine may cause bladder cancer. Bonser in 1943 produced cancers of the bladders in dogs by feeding 2-naphthylamine over a period of several years. A detailed study of the intermediate and excretion metabolites led the authors to conclude that 2-amino-1-naphthol is the compound responsible for these occupational cancers.

Bonser, G. M.; Clayson, D. B.; Jull, J. W., and Pyrah, L. N.: Experimental industrial cancer. Brit. J. Urol. 26:49-52, March, 1954.

Atomic Radiation and Cancer

The report of the Committee on Pathologic Effects of Atomic Radiation contains several important references to neoplastic disease. Some late effects of radiation appear as leukemias, which are found to

arise a few years after exposure. This disease may show manifold increase in persons subjected to a nearly fatal dose or in those whose occupations have exposed them to dose rates beyond those acceptably permissible. Cancer has been induced in animals given overwhelmingly large oral doses of insoluble isotopes. Radiation effects on the skin consist of a transitory erythema resembling sunburn the first day. A few days later a more persistent erythema associated with pigmentation appears. High doses may cause ulceration at this stage. Much later intractable ulceration with atrophic changes and marked blood-supply deficiency is seen. Such chronically damaged skin is a fertile bed for the development of cancer. Widespread changes including bone sarcoma are likely to appear as late effects of radium poisoning after repeated bone destruction and repair. In the lung radiation results early in congestion and increased secretion, and late in fibroma and the development of cancer as was shown among miners inhaling high concentrations of radon gas. Leukemias have followed heavy radioiodine treatment of hyperthyroidism, and a small proportion of children treated with roentgen rays to the upper part of the body develop cancer of the thyroid later on, suggesting high sensitivity of the child's thyroid.

[Report of the Committee on Pathologic Effects of Atomic Radiation, Warren, S., Chairman]: Pathologic effects of atomic radiation. Science 124:60-63, July 13, 1956.

Cancer in Jute Workers

At the Dundee Royal Infirmary, from July, 1952 to August, 1953, among a total of 17,800 jute workers sixteen had dermatitis, five oil acne, and ten premalignant or malignant skin changes including atrophy, pigmentation, keratoses, purpura, telangiectases, and epitheliomas of the face, forearms, and hands. Two men had scrotal carcinoma. Skin affections were four times as frequent among jute workers as among patients not engaged in the jute industry. Premalignant changes were found in women more often than in men, and in older than in younger workers. Spinners have a particularly high relative frequency of carcinomas which are radiosensitive and highly malignant. It is uncertain if the skin damage is done by the batching oil, the lubricating oil, or the jute itself. Protective creams and appropriate hygiene are advised in prophylaxis.

Kinnear, J.; Rogers, J.; Finn, O. A., and Mair, A.: Dermatoses in jute workers. Brit. J. Indust. Med. 12:36-42, Jan., 1955.

Buyo Cancer of the Cheek

Cancer of the cheek, commonly seen in the Philippine Islands, is caused by chewing buyo—a mixture of betel nut, buyo leaves, tobacco and lime. The lime is the active etiologic agent. Buyo cheek cancer is a definite and separate disease of Oriental tropical peoples, having an entity as distinctive as the epithelioma occurring on the hands of the early workers with roentgen rays, as the kangri skin cancer of India, as the skin cancer on the arms of paraffin workers, as the cancer of chimney-sweeps in England, and as the brand cancer of cattle in the United States. It is an epithelioma produced by chronic chemical irritation of the lime. Treatment is unsatisfactory and control consists in encouraging prophylaxis. As in other forms of cancer where the cause is definitely known, complete control could be obtained by an entire stopping of the buyo habit.

Davis, G. G.: Buyo cheek cancer; with special reference to etiology. J.A.M.A. 64:711-718, Feb. 27, 1915.

Iatrogenic Cancer

Ionizing radiation is too potent a tool to use in non-malignant disease except under the most compelling clinical indications.

—Raventos, A.: Should we stop treating children with X-rays? Weighing the benefits against unknown dangers. [Editorial.] Pennsylvania M. J. 59:1155-1156, Sept., 1956.

Non-Occupational Aspects of Environmental Cancer

E. L. Wynder, M.D.

"I had an interview with the Board of Guardians of St. James Parish . . . in consequence of what I said, the handle of the pump was removed the following day." These words of Snow record a historical event in man's fight against cholera and at the same time present a classical example of epidemiological technique and its role in determining the cause and prevention of disease in man. To be learned from Snow's observations is the fact that a pathogenesis of a disease does not have to be known in its entirety in order to permit its prevention, and that preventive measures do not have to eliminate all the disease in order to be practical.

While the basic factors of cancer causation remain a puzzle a large variety are known to play a role in the formation of cancer in man. Initially these were limited primarily to industrial types of cancers where effective preventive measures have already been followed by satisfactory results. From these studies we know that many factors can induce the same type of cancer and that not every individual exposed to these factors will develop cancer. These truisms, of course, apply to almost any disease. Not every person, for example, exposed to the polio virus will develop poliomyelitis. In this connection we have stated a number of postulates which establish a given factor as a carcinogen to man:

1. The relative risk must rise in proportion to the degree of exposure.
2. Rates among specific population groups must be consistent with the distribution of the agent.
3. Withdrawal, reduction, or modification of the agent in a population group must be followed by a decrease in incidence of a given cancer after a suitable latent period.
4. The agent should be shown to be carcinogenic to some animal species (not obligatory).

In this light, we shall briefly review the most pertinent nonindustrial factors playing a role in the induction of cancer in man.

Tobacco. Much evidence indicates that tobacco and its various products constitute an important carcinogenic factor to man. In the form of cigarette smoke inhaled it appears to be responsible for 80 per cent of all bronchiogenic cancer as it occurs in man today. This fact is borne out not only by numerous retrospective and prospective studies but is consistent with the sex distribution, the age level and the geographic pattern of lung cancer. It is consistent with the long-held view that pyrolysis of various substances, even of simple structure, leads to the formation of polycyclic aromatic hydrocarbons which we recognize to be carcinogenic. In the upper respiratory tract we find smoking to be of equal importance as in lung cancer; however, we find a change in the type of smoking predominantly used. For intrinsic-larynx cancer the smoking pattern of cigarettes, pipes and cigars is like that for lung cancer. In extrinsic-larynx cancer pipe and cigar smoking are of somewhat greater importance, and in cancer of the oral cavity the relative risk of pipe and cigar smokers to develop cancer in this area is greater than that of cigarette smokers. In cancer of the oral cavity, particularly cancer of the tongue and buccal mucosa, tobacco chewing is also of some though lesser importance. In view of the fact that cancer of

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the upper alimentary and respiratory tracts make up a major proportion of all cancers in man, it can be seen how practical preventive measures directed against the use of tobacco are of paramount importance. These measures include moderation of smoking habits, "effective filtration," the level and meaning of which remain to be defined, a modification of pyrolysis and a removal of substances which upon pyrolysis may act as precursors to carcinogens.

Alcohol. Alcohol, particularly in terms of heavy whiskey consumption, has been demonstrated to play a role in the development of cancer of the larynx especially of the extrinsic type. In contrast to the studies of smoking and cancer where an increased risk is already demonstrable at the lower levels of tobacco consumption, this risk increases only with consumption of 7 or more ounces of whiskey a day. An even more pronounced effect of alcohol consumption has been found in recent studies of cancer of the oral cavity. It remains to be determined whether alcohol acts as a promoting factor or whether it can initiate cancer on its own. This point is difficult to determine statistically in view of the fact that very few heavy drinkers are nonsmokers. From the point of view of prevention, however, it is only academic whether a factor initiates or promotes cancer. In either case its successful control will decrease cancer incidence.

Nutrition. Relatively little is known about the influence of nutrition on cancer formation in man. Life insurance companies' statistics indicate that certain types of cancers are more prevalent among people who are above average weight. There is a suggestion that population groups living in iodine-poor districts have not only an elevated rate of goiter but also a higher incidence of cancer of the thyroid. Severe nutritional deficiencies, particularly in respect to vitamin B complexes, may predispose to cancer of the liver as indicated by data from Africa, although it would appear that other factors, as yet of unestablished nature, are of importance as well. Perhaps the best evidence linking nutritional deficiency with cancer formation in man comes from studies linking Plummer-Vinson's disease, primarily a chronic iron deficiency state, to cancer of the upper alimentary tract. This association has now been well established. It would appear, however, that in addition to iron deficiency, deficiencies of other nutrients may be of additional importance. At any rate these data, which have been chiefly collected in Sweden, clearly indicate that nutritional deficiency may act as a precursor to cancer.

Recently much publicity has been given to various food products, and food dyes and additives as possible causes of cancer to man. Evidence so far available applies primarily to animal experimental data.

It remains to be resolved whether laboratory tests conducted with more sensitive animal tissue justify the conclusion that damage can come to human tissue. The primary criteria to establish carcinogenicity for any material in man must be human epidemiological data. For instance, since there is little evidence that excessive hormone intake as medication initiates cancer in man, there seems little reason to worry about the occasional intake of chicken meat upon feeding the animals estrogens. These, perhaps negative thoughts, are merely indicated so that we do not unnecessarily confuse the public about the possible dangers of extrinsic factors but point out the need for criteria which have to be met in order for a given substance to be regarded as carcinogenic to man. Once we have agreed upon these criteria we should be prepared to accept these for all factors to which man is exposed. At the same time, it would seem advisable to avoid food products for which there is a significant degree of animal experimental evidence that they produce cancer particularly if they can be replaced just as easily by alternative substances. In cancer prevention we must avoid excessive concern as much as we must avoid too little concern.

Smegma. Smegma, or its decomposition products, has been first suspected as a cause of cancer in man because of its apparent role in the formation of cancer of the penis. Since penile cancer, however,

has not been very prevalent in the Western hemisphere this problem has never received the attention it should. Since recent data have indicated that smegma may be of equal importance in the formation of cancer of the cervix the subject has been reopened as a point of general interest. The two factors found to be most important in the development of cancer of the cervix are the age at first intercourse and the penile hygiene of the sexual partner. In view of the fact that the first of these factors does not allow for a practical solution the second factor gains importance. Available statistical and epidemiological data suggest that universal circumcision would decrease the incidence of cancer of the cervix by 80 per cent. If the incidence of cancer of the cervix in the general population were the same as it is among Jewish women this type of cancer would be no particular problem

Other factors. AIR POLLUTION has been considered to be a factor in the development of cancer of the lung. A study by the American Cancer Society shows the rate of lung cancer among city dwellers to be somewhat higher than that among rural dwellers with similar smoking habits. The factor of air pollution is not consistent with the age distribution of lung cancer or with its sex ratio. In any study on air pollution it is important to consider the factor of occupational exposures, since certain occupations are known to increase the risk of lung cancer. Since these occupations are more common in large cities one has to standardize for this factor in order to define more clearly the effect of air pollution. The total present evidence suggests that air pollution may play some role in the development of lung cancer in some larger cities but that in the over-all lung-cancer problem as it occurs throughout countries and population groups it is of secondary importance.

Among other non-industrial factors is the obvious effect of excessive SUNLIGHT on cancer of the skin, the data from which are based primarily on the geographic and anatomic pattern of skin cancer. SYPHILITIC GLOSSITIS is a factor in the development of cancer of the anterior two-thirds of the tongue. In recent studies we have found that 35 per cent of patients with this type of tongue cancer gave a history of syphilis.

Studies on breast cancer have suggested that lack of early LACTATION may increase the chance of a given mother to develop breast cancer. This seems consistent with the fact that during the past 30 years the mortality of breast cancer has steadily increased in the United States, during a period when breast feeding has become increasingly less common. If statistical studies currently being conducted can confirm this point of view then we are confronted with another very important way of reducing the major type of cancer in women.

HUMAN MILK has been considered to be a factor in the development of breast cancer in man largely on the basis of work with mice which established a transmissible milk factor. However, the available human data do not indicate that nursing increases the likelihood of breast cancer in the offspring. A great deal of debate has centered about the role of HORMONES in the development of cancer in man particularly in cancers of the breast, uterus and prostate. Though there are a few cases on record for these sites in which patients had received high dosages of estrogens prior to developing one of these cancers it is the current consensus that these hormones do not play a significant role in the initiation of cancer in man, though it remains to be ruled out that they can play a promoting effect upon cancers already initiated.

Among other nonindustrial factors suspected to play a role in the development of cancer is the parasitic disease SCHISTOSOMIASIS. There is fair evidence that it plays a part in the development of bladder cancer in Egypt. Its role in the development of liver cancer in Japan and Africa is less certain.

Relatively little is known about factors playing a role in the development of cancer of the lower gastrointestinal tract. A number of factors are suspected but much more information must be accumulated before we can incriminate any particu-

lar factors with any degree of reliability.

BETEL-NUT CHEWING is undoubtedly a common cause of cancer of the upper alimentary tract in India. It remains to be shown whether tobacco has to be an integral part of the betel-nut quid in order for it to be carcinogenic to man.

HEAT has been mentioned as a cause of cancer. Though a scar resulting from a burn is to be regarded as a precancerous lesion there is no evidence that heat per se can induce cancer in man. Most of the suspicion in this regard has been based on the belief that the heat of a pipe stem can induce cancer of the lip. There is no evidence to support this view.

There are two factors which, though never established as playing roles in the development of cancer, are frequently mentioned by physicians and particularly by lay people as causes of cancer. PREGNANCY, for one, has often been thought to be a cause of cancer of the cervix. It is indeed true that patients with cancer of the cervix have a higher parity than control patients. This, however, is due to the fact that patients with cancer of the cervix tend to marry earlier and belong to a lower socioeconomic group, both of which factors increase the number of pregnancies. It has now been established that if one standardizes for these two factors women with cancer of the cervix have the same number of children as control groups. Thus, neither pregnancy nor any of the other gestation processes appear to be of any significance in the production of cancer of the cervix. The data on pregnancy show the importance of carefully conducting statistical analyses which can separate the factors which are of primary, secondary, or no significance.

TRAUMA is frequently mentioned as a cause of cancer in man, particularly as it applies to cancer of the breast. Whereas trauma may first call attention to an already existing cancer and while it is conceivable that trauma can promote an already initiated cancer, there is no evidence that trauma per se can initiate cancer in man or in the experimental animal.

In general it may be said that there is much fact but also much folklore associating certain environmental factors with the development of cancer in man. It remains to the researchers in the field of statistics and epidemiology to separate them.

Animal research. The primary purpose of animal research in the field of cancer causation is to establish mechanisms and define specific carcinogens as they apply to a specific animal and animal tissue. Once such results have been obtained one can only assume that the carcinogens responsible for the tumors in the animal are also responsible for the tumors in man. The final proof, however, as to whether the material produces cancer in man can come only from human statistical and epidemiological data. If an animal experiment is negative this does not prove this material to be safe for man. On the other hand, if a material produces cancer in animals it does not by itself prove that it can also induce cancer in men. What is necessary is a combined approach to the problem, that is, from the point of view of human as well as animal data. If an agent thought to be carcinogenic to man is also found to be carcinogenic to a variety of animals and animal tissues then the animal data gain much in significance. If the human data are at hand first then animal experiments must be designed to elucidate the effect and mechanism of the specific substance in question. On the other hand, if the suspicion is first raised on the basis of animal experience, detailed epidemiological studies have to be carried out before we can definitely incriminate this material to be carcinogenic to man. In the final instance we need a close collaboration of human and animal research and the modern epidemiologist should have training, time, and space to approach the problem from both points of view.

Causation. One often hears "how can one talk about cancer causation if in fact we do not know the cause of cancer?" The term causation refers to a multiplicity of different factors which together cause a disease. Even in the field of bacteriology or toxicology, which have greater specificity, we deal with host factors which determine a given disease process. In the

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Figure 1. Merchant seaman and constant tobacco smoker, chiefly pipe, with squamous-cell carcinoma of lower lip. Pipe smoker's carcinoma of the lip has long been known but whether the etiologic factor is irritation, heat, or carcinogenic tar is still unknown.

Figure 2. Seventy-three-year-old farmer with basal-cell carcinoma of the nose.

Figure 3. Oysterman and fisherman, 63 years of age, from Great South Bay, with multiple, recurrent skin cancers of the face and hands. Outdoor exposure and solar radiation may represent co-carcinogen effects.

Figure 4. Crude-oil–refinery laborer with squamous-cell carcinoma of the lip, basal-cell carcinoma of the skin of the face, and multiple areas of keratosis.

Figure 5. Radiation-induced squamous-cell carcinoma with metastases to neck nodes in patient treated thirty-five years before by radiologist for acne.

Figure 6. Radiation-induced basal-cell carcinoma in patient treated for superfluous hair with low-voltage roentgen ray by beauty operator twenty-one years before.

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Figures 7 and 8. Seventy-eight-year-old fisherman, older of two brothers both with recurrent, multiple skin cancers. *Left:* Squamous-cell carcinoma of lip. *Right:* Basal-cell carcinoma of thumb. Hauling of tarred lines and outdoor exposure may enhance carcinogenic action.

Figures 9 and 10. Betel-nut cancer. The betel cud contains areca nut, betel leaf, lime, and sometimes tobacco. Cancer results oftener when tobacco is a constituent. *Left:* Betel-nut chewer's carcinoma of the cheek in an East Indian. *Right:* Betel-nut cancer attached near angle of the mandible.

Figures 11 and 12. Mule spinner's cancer. These skin carcinomas, formerly occurring on the lower abdomen, thighs, and genitalia following prolonged exposure to the oils used to lubricate the spinning mule, are now prevented by protective and hygienic measures and by the substitution of other lubricants for the more highly carcinogenic shale oils. *Left:* Mule spinner's cancer of the penis. *Right:* Spinning frames reducing size of loosely twisted strands of cotton into threads.

Figures 1 to 8. Courtesy of Dr. Oliver Moore, Head and Neck Service, Memorial Center for Cancer and Allied Diseases, New York City.

Figures 9 to 12. Courtesy of Armed Forces Institute of Pathology, Washington, D. C.

more unknown realms of cancer one is confronted with additional unknowns. But it is not necessary to know and understand each given step in the pathogenesis of a disease in order to prevent it. If we can remove one factor that plays a role in the development of disease, we can decrease its incidence. If this factor is of primary importance we might eliminate the disease and if it plays the role of a catalyst we might merely reduce it, in either case a desirable event. This field has unfortunately received a great deal of emotional argument because of the data linking smoking to lung cancer and many of the principles, long regarded as established on the basis of industrial cancer data, are now being forsaken on the basis of "saving tobacco." For instance, one often hears even from medical colleagues that not every one who smokes develops cancer of the lung, larynx or mouth and that they know individuals who have smoked heavily for years who have never developed cancer. Such happenings are also seen with cancer types where everyone, at least in the past, agreed that they were induced by a given factor. For instance, not every exposed aniline worker will develop bladder cancer, and bladder cancer may arise in people not exposed to aniline dye. X-radiation, certainly an established cause of cancer, will not cause cancer of the skin or leukemia in every radiologist—these cancers may arise in people not exposed to radiation. Similarly, we must expect lung cancer in nonsmokers, though this occurs rarely, and that there are other factors that may also initiate lung cancer. These points agree with every established principle of carcinogenesis be it in man or the experimental animal.

Statistical data in the final instance represent a given risk of an individual exposed to certain factors to develop a disease. If these statistics are carefully obtained, if they are repeated under different conditions and, above all, if they are in line with the epidemiological pattern of a disease, they must be regarded as a proof of causation of a given disease and the burden of proof lies upon the person who claims this to represent a mere statistical artifact. At times too one hears, unfortunately again among medical colleagues, that statistics can prove anything. Such statements are most frequently made by people who are not aware of the principles of statistics and that in its pure form statistics is as much of a science as mathematics, physics and chemistry. It is particularly unfortunate, however, that the same individuals tend to accept the statistics of an association they want to believe while refuting the ones that do not appeal to their emotions. For instance, the medical profession is quite ready to accept statistics showing that children vaccinated with Salk's vaccine have a 4-times lower incidence of poliomyelitis than those who have not been vaccinated, while at the same time ignoring the statistics of the American Cancer Society which indicate that persons smoking 2 packs of cigarettes a day have 70 times the incidence of lung cancer as the nonsmoker. In comparative terms this increase in incidence for lung cancer is so enormous that it staggers the imagination. No statistical errors have been determined in this study which could account for a difference of this magnitude.

In this discussion we have briefly outlined some of the factors which play an important role in the development of cancer in man which are of general significance. We have referred to the roles that statistics, epidemiology and animal research play in this field and have indicated the great reduction that can be obtained in certain forms of cancer through practical preventive measures. We are aware that some of these measures involve factors which are difficult to institute because of economic or emotional pressure. However, if we face the problems squarely even these more difficult tasks can be overcome through practical ways. For physicians and scientists interested in cancer research and in the control of cancer in man there is only one task—and that is to try to the best of our ability to establish ways in which we can prevent cancer in this and in future generations.

Environmental Aspects in the Etiology of Occupational Cancer

*Arthur J. Vorwald, Ph.D., M.D.**

Epidemiologic studies indicate that cancer afflicts human subjects in almost every part of the world and that no race is immune to the disease.

It is also evident that certain tissues and organs develop cancer because of prolonged exposure to certain chemical and physical agents which gain access to the body from outside sources and which alone, or in combination, have the biologic capacity to invoke cancer. Accordingly, those agents are identified as exogenous or extrinsic causes. The resultant cancer is frequently labeled as environmental and in the case of the worker exposed to such agents in connection with his job, the cancer is designated as occupational.

Although a number of extrinsic agents have been unequivocally identified in the causation of occupational cancer and while the carcinogenic role of numerous other agents is only suspect, and in many instances is based solely on experimental evidence, there is mounting concern regarding the possible existence of many additional extrinsic agents which remain undetected and which may bear a cause and effect relationship in the etiology of human cancer. Since knowledge of cause and effect is a basic requirement for prevention of disease, it is obvious that studies focused on the detection of such agents constitute a most important approach for the control of cancer.

Studies of the environment with respect to cancer and other tumors of occupational origin, may be undertaken from a number of different but interrelated points of view. Basically, they may be either experimental or clinical, may have reference to cancer in general or may pertain to specific tissues and organs of the body such as the skin, the lung, the bone or the blood. Many notable observations have been made in each of these categories.

Experimentally, a wide variety of chemical and physical agents have been tested for carcinogenic activity in animals.[29, 30] The list of more than 500 active carcinogens is impressive, and includes the following: a number of inorganic substances in the form of metals, oxides, cations and anions; many organic substances such as aliphatic hydrocarbons, aromatic monocyclic, polycyclic and heterocyclic hydrocarbons, aromatic amines, azo dyes, steroids; thermic, ultraviolet, and ionizing energies; and viral agents. A few illustrations as typical examples, having possible relationship to occupational cancer, are appropriate.

Among the inorganic substances, various compounds of beryllium have been shown by a number of investigators to produce osteogenic sarcomas in rabbits after repeated intravenous injection.[19, 24, 74] Metallic chromium induces osteogenic sarcomas at the interosseous site of implantation in rabbits.[67] Pure powdered metallic nickel suspended in lanolin is productive of sarcomatous lesions at the site of implantation in the marrow cavity of the femur, the pleural cavity and the nasal sinuses of female albino rats.[41] Selenium fed orally to rats causes the development of adenomas and low-grade carcinomas in the liver and also adenomas in the thyroid of rats.[64, 69] The intratesticular injection of zinc chloride into fowl is followed by the development of testicular teratomas.[21, 22] The topical application of arsenical compounds provokes papillomas in the skin of rabbits.[14]

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With respect to organic agents, the past several years have seen many accessions to the list of chemicals which have been shown to produce cancer in various organs and tissues of a variety of animal species including the mouse, rat, hamster, guinea pig, rabbit, dog and porcine pig. Among such chemicals the aliphatic and aromatic hydrocarbons, including amines and azo dyes, are most conspicuous numerically. One or the other of these agents, either free or combined with other substances, attends a variety of many occupational pursuits especially those which provide prolonged contact with pitch, coal tar, waxes, paraffin oil, creosote, anthracene oil, high boiling fractions of petroleum and of shale oils, greases, degreasing compounds, dyes and related products. Specific enumeration of each of the chemicals with respect to experimental carcinogenicity is beyond the limited scope of this presentation. However, certain experimental results may be briefly cited: β-naphthylamine in the production of bladder cancer in dogs;[6, 46] trypan blue and hepatic sarcoma in rats;[25, 72] various aromatic hydrocarbons and cancer of the skin in a variety of animal species including mice, rabbits and monkeys.

The literature contains many reports of experimental studies concerning the cancerogenic and leukemogenic action of various environmental agents of a physical nature which have occupational connotations. For example, cancerous effects have been noted in the skin of white mice exposed to ultraviolet radiations as derived from solar and artificial sources.[32] Similar untoward effects have been elicited in target tissues of experimental animals exposed to ionizing energies of various types and from numerous sources such as emanate from radiation-generating devices or from natural or artificial radioactive substances. In this regard a few examples are cited, as follows: x-rays and cancer of the skin in addition to leukemic conditions in mice;[33, 34] P^{32} and carcinomas and sarcomas of the skin in rats;[36] mesothorium, plutonium, radium, radon, thorotrast, uranium, Ce^{144}, Pr^{144}, Sr^{89} and osteogenic sarcomas in mice, rats and rabbits;[7, 8, 9, 17, 18, 20, 23, 44, 48, 55, 68, 70] radioactive iodine and cancer of the thyroid in rats and of the hypophysis and trachea in mice.[13, 16, 27]

The foregoing is a brief presentation of only a few observations concerning the tumorogenic action of certain agents which may be present in the environment and which may have reference to occupation from an experimental point of view. Clinically, the various aspects of environmental carcinogens with respect to occupational cancer have been the subject of extensive studies and reviews.[40, 42, 43, 45] Although not all investigators will agree with all of the evidence presented to support the occupational thesis in the etiology of many of the clinical cancer cases which are cited in those reviews, "the conclusion is inescapable that exogenous agents, particularly of industrial origin, are important factors in the causation of certain types of cancer."[40]

In the case of lung cancer, a disease which at present constitutes the major problem in the field of pulmonary diseases, the causative factors are indeed the subject of much current debate. Although it is generally recognized that the responsible agent or agents are predominantly extrinsic, and in most instances gain access to the respiratory tract and lung by way of inhalation, there is divergence of opinion regarding the absolute etiologic significance of inhaled cigarette and/or tobacco smoke in contrast to inhaled environmental pollutants which contaminate the general atmosphere, or which are incidental to certain occupations.

Much of the debate stems from the reasoning that the current high frequency of lung cancer in man requires an agent or agents which attack a large part of the male population. Cigarette smoke and certain pollutants of the general atmosphere seem to satisfy this requirement. However, there is disinclination on the part of some observers to incriminate occupational pollutants because of their belief that the number of male employees exposed to the inhalation of occupational carcinogens and ultimately developing occupational pulmonary cancer is too small

Table of Environmental Agents in the Etiology of Malignant Tumors
Carcinoma — Sarcoma — Leukemia

(An appraisal of current evidence having possible relation to occupation.)*

AGENT	EXPERIMENTAL (Lab. Animals)	CLINICAL (Human Subjects)
INORGANICS		
METALS		
arsenates	+	+
beryllium	+	O
cobalt	+	O
chromium	+	O
chromates	+	+
copper	+	O
nickel	+	+
selenates	+	O
zinc	+	O
POLYMERS		
asbestos	?	?
silicones	+	?
ORGANICS (also Intermediates and Derivatives)		
ALIPHATIC		
acetyl choline	+	
carbon tetrachloride	+	
diethylene glycol	+	
dichloro-N-methyldiethylamine	+	
ethyl carbamate	+	
epoxides	+	
diepoxides	+	
ozonides	+	
AROMATIC HYDROCARBONS		
MONOCYCLIC		
benzene	+	
benzidine	+	
chlorophenothane (DDT)	+	
o-toluidine	+	
p-hydroxyhexane	+	
triphenylethylene	+	
triphenylbenzene	+	
POLYCYCLIC		
anthracene	+	
acenaphthene	+	
acenaphthanthracene	+	
benzanthracene	+	
benzphenanthrene	+	
benzanthrone	+	
benzpyrene	+	
chrysene	+	
cholanthrene	+	
dibenzanthracene	+	
fluorene	+	
pyrene	+	
HETEROCYCLIC		
benzacridine	+	
benzcarbazole	+	
triophanthrene	+	
QUINONES		
α-napthoquinone		
AMINES		
aminofluorene	+	
aminobenzanthracene	+	
β-naphthylamine	+	
TRIPHENYL METHANE DYES		
fast green	+	
light green	+	
methyl blue	+	
AZO DYES		
aminoazobenzene	+	
aminoazotoluene	+	
scarlet red	+	
sudan III	+	
STILBENES		
dihydroxydiethylstilbene	+	
STEROIDS		
cholestadiene	+	
desoxycholic acid	+	
estrone	+	
progesterone	+	
testosterone	+	
PHYSICAL		
Mechanical Trauma	?	
Thermic Energies	?	
Ultraviolet Energies	+	
Radioactive Energies	+	
†VIRUSES	+	

Many of these agents may not be present in isolated form as a contaminant of the environment and thus their specific action in human carcinogenesis cannot always be established. However, there is clinical evidence for the carcinogenic action of their combination in different ratios as may occur in a variety of occupational exposures involving prolonged contact of the body tissues with chemically complex substances such as: coal tar, asphalts, pitch, creosote, soots, waxes, paraffin oils, spindle oil, shale oil, lignite oil, petroleum oil, anthracene oil, lubricating oil, cutting oil, quenching oils, crude mineral oil, coke and gas retort effluents, fumigants, raw materials for carbon black and lamp black, coal combustion products, rubber plasticizers, lacquers, paints, etc. The itemized list includes agents which may be constituents of synthetic polymers (polyethylene, cellophane, bakelite), textile and food dyes, food preservatives, various agents used for medicinal purposes, etc.

*The table cites only the documented evidence concerning some of the more important agents, especially among the classes of organic compounds.

†Direct action unproven. (The thought is entertained that occupational agents of a chemical or physical nature may stimulate viruses in tissue or may adversely alter the tissue resistance to them. Parallel effects are seen in the case of free crystalline silica and tubercle bacillus infection.)

to account for more than but a very minor segment of the total number of men afflicted with lung cancer. This belief implies a knowledge of all of the past and current environmental agents of occupational origin which have a direct or indirect (cofactor), an additive or synergistic, promoting or anticarcinogenic action in the development of lung cancer. This belief also postulates that occupational and non-occupational cancer of the lung is being adequately detected in male subjects of the working population. Furthermore, this belief assumes that occupational exposures to a polluted atmosphere do not constitute a sufficiently impressive denominator which is common for male subjects who develop cancer of the lung. In my opinion, these beliefs are untenable.

Experimentally, numerous attempts have been made to induce cancer of the lung in animals. For the most part, efforts in this regard have been unsuccessful for lack of the experimental tools and methods deemed adequate for study of the pulmonary carcinogens that may operate in man. Basically, this stems from the fact that in many respects the milieu of the experimental animal differs so remarkably from that of man. Furthermore, the experimental method is complicated by many imponderables such as the proper selection of species and strain of animals, materials for test, dosage levels and length of test, and the routes of administration which may parallel the circumstances, albeit frequently unidentified, attending human carcinogenesis.[71] These complications accompany almost every experimental venture involving the use of animals for assay of biologic activity of a substance in terms of human experiences, and certainly the difficulties are not unique for studies pertaining to cancer. Animal experiments are extremely important, if for no other reason than to understand more fully the mechanisms which operate in the development of cancer and to provide the clue for its prevention and control in human subjects. Nevertheless, it should be emphasized that positive or negative results with animals are not totally definitive for man and that extreme caution must be exercised when interpreting experimental results in terms of human cancer. From these considerations it is obvious that any final decision regarding the causation of cancer of the lung in man must be supported by sound clinical evidence.

During the past several decades, biologic experiments for the study of carcinogenesis have predominantly utilized the mouse as the test animal. The mouse, however, is not the most ideal subject for studies concerning pulmonary cancer because of the spontaneous tumors that occur so commonly in the lung of certain inbred strains. This feature is not altogether undesirable since the mere spontaneity of these tumors in the mouse makes this animal an extremely sensitive subject for the biologic testing of agents which may have a low degree of carcinogenic activity in the lung. The importance of an adequate control group is quite apparent.

With respect to mice, a significantly higher incidence of alveologenic carcinoma has been induced by exposing them to agents relevant to man's occupations. The list of these agents includes: powdered metallic nickel;[10] iron oxide;[10] many aromatic hydrocarbons and their derivatives such as 3,4,-benzyprene; 1,2,5,6-dibenzanthrene; 20-methylcholanthrene; 3,4,5,6-dibenzcarbazole; 2-amino-5-azotoluene; 9,10-dimethyl-1,2-benzanthracene; ethyl carbamate;[65] ozonized gasoline;[50] nitrogen mustard;[38] sulphur mustard;[37] and ionizing radiations.[35, 47, 58, 66] Similar results have been obtained in mice exposed to complex substances such as aerosols of tar.[11, 12, 54]

The preceding review is somewhat incomplete and indeed would be more so by failing to cite an important observation, namely that squamous-cell cancers are induced in the lung of mice by implanted silk threads impregnated with dibenzanthrene.[3]

In contrast to the mouse, spontaneous pulmonary tumors are rarely observed in the rat, and for that matter in the majority of other species of animals. In them,

therefore, the induction of pulmonary tumors, by environmental agents possibly attending occupation, is significant. This has been accomplished by exposing rats to urethane.[63] An inhaled aerosol of radioactive cerium has produced metaplastic changes in the bronchial epithelium and the development of malignant tumors in rats.[55] Ionizing radiations and polynuclear hydrocarbons, impregnated on thread or in stainless steel pellets and introduced into the lung or bronchus of rats, have provoked bronchogenic cancer comparable to that seen in humans.[53] Soluble and insoluble compounds of beryllium, such as the sulfate or the oxide, when introduced by intratracheal injection or by way of inhalation into the lung of rats, have induced pulmonary adenocarcinoma and squamous-cell carcinoma with metastases to the tracheobronchial lymph nodes, parietal pleura, mediastinal connective tissue and diaphragm.[73, 74, 75]

Clinically, a causal connection between environmental agents and cancer of the lung in human subjects is indicated by a number of observations.[39, 43, 49] The data presented are most impressive and in many respects certainly support the view that respiratory hazards do exist which are responsible for cancer of the lung. It must be admitted, however, that the human evidence with respect to occupation is predominantly epidemiological and in many instances is compiled from rather limited case studies and experiences. Evidence discloses a firmly established causal relationship for only a few substances in certain occupational situations. These pertain to nickel,[62] chromates,[1, 2, 4, 5, 28, 60, 61] and radioactive substances.[29, 57, 59]

In my opinion there are many other occupational situations which are high on the list involving suspected, but as yet unproven, carcinogens in the etiology of lung cancer. These situations expose workers to aerosols that attend the processing and use of: asbestos;[15, 26, 62] certain aromatic hydrocarbons such as derived from the distillation and incomplete combustion of petroleum, oil shale, natural gas, coal and tar.[14]

In this brief review an endeavor is made to analyze occupational cancer from two broad approaches, namely the experimental and the clinical. Irrespective of the approach, it is apparent that studies of the environment in the interest of cancer, and especially of the lung, are frequently complicated by a host of variables which cannot always be determined with certainty in the light of present knowledge. Some of the most obvious variables pertain to the widespread distribution of agents which contaminate the environment, their almost infinite variety and concentration in many obscure physical and chemical combinations under ever-changing conditions, the difference in their mode of entry into the body and in their capacity to irritate tissue and to provoke cancer. The studies are further complicated by the divergent susceptibility of different persons to similar irritants, the varied intensity of their exposure in terms of dosage and duration as may be defined by the unstable environment which so frequently attends one's work and life habits, the long interval of time which so often intervenes between exposure and definitive diagnosis of cancer. Furthermore, and with particular reference to occupation, a number of most vexing problems are posed by these considerations; namely, that although some individuals develop cancer because of occupational exposure to one or a number of carcinogenic agents, it is equally true that certain individuals exhibit cancer which has no apparent occupational relationship to such agents, and that irrespective of exposure to known carcinogenic agents, many individuals remain free of cancer. Finally, while it cannot be denied that environmental cancer occurs it must also be admitted that in many respects the full elucidation of occupational cancer awaits further refinement of experimental, clinical and epidemiological studies.

(For references see following page)

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Iatrogenic Cancer

Dr. Winship has requested that, in the abstract of the article on thyroid carcinoma in children by him and Chase, the last sentence on page 80 of the May, 1956 issue of *CA: Treatment by radiation during infancy for enlarged thymus is shown definitely to be an etiological factor*, be changed to read: *There is a considerably higher prevalence rate of thyroid carcinoma in children treated by radiation to the neck region than would be expected in a group of nonirradiated children.*

Of further interest in this connection is the report in *Clin. Proc. Child. Hosp.* (Washington, D. C.) *11:* 209, Oct., 1955, of a discussion of the irradiation effects of therapy of the thymus gland in relation to the production of thyroid carcinoma, at a meeting of the Tumor Board of that hospital on September 14, 1955, Dr. Lattman, Radiologist, presiding:

DR. WINSHIP: "Counting all the known cases in the United States, of childhood with carcinoma of the thyroid, almost 20 per cent have had irradiation to the thymus gland or to the neck for some other disease. This is a significant percentage. These figures should be recalled when we plan to irradiate a child who has difficulty in breathing. Court-Brown and Abbatt [*Lancet 1:* 1283, 1955] . . . found that 25 of the 2361 patients with ankylosing spondylitis, treated with x-rays, developed leukemia. The expected rate of leukemia for a group of this size was 3.9 patients. I mention this only because the results are similar to those in children irradiated for thymus enlargement who develop thyroid carcinoma . . . in the city of Washington during the past ten years there have been ten cases of thyroid carcinoma in children and three of them had irradiation of the thymus gland."

DR. KLOPP, referring to the practice of irradiating for tuberculosis of the cervical lymph nodes, acne, tonsils and adenoids, and heavy beard: "Irradiation is potentially very dangerous and we should use it very, very carefully. The percentage is higher than found by Dr. Winship and would be still higher if we had the correct information."

Dr. Morris Fishbein, in *Postgrad. Med. 20:*446, Oct., 1956, reviewed the report of D. E. Clark before the Chicago Surgical Society meeting, May 6, 1955. Of thirteen cases of cancer of the thyroid three had had irradiation for enlarged thymus, three for cervical adenitis, five for enlarged tonsils, one for peribronchitis, and one for persistent pertussus. Age at the time of irradiation ranged from two months to six years, and at the time of histologic diagnosis from four to fifteen years. The current increase in the incidence of carcinoma of the thyroid corresponds to the period when irradiation was being widely used for benign conditions of the head, neck and thorax. Dr. Fishbein comments that while the evidence is small in amount and obviously statistical, the observations support the concept that there may be an association between prior irradiation and cancer of the thyroid in children and adolescents.

Majarakis, Slaughter, and Cole [*J. Clin. Endocrinol. 16:*1487, Nov., 1956] found that of ten patients with thyroid cancer 15 years of age or younger, all had had x-ray therapy to the head and neck an average of approximately eight years previously. None of five patients with thyroid cancer and older than fifteen years had been irradiated.

Stewart, A., et al., in *Lancet 2:*447, Sept. 1, 1956, reported that in two comparable groups of mothers—one given, and the other not given, antenatal roentgen-ray examinations—forty-two children in the irradiated group and but twenty-four in the nonirradiated group died of leukemias, and that forty-two children in the irradiated group and but twenty-one in the control group died of other malignant disease. These figures indicate that diagnostic pelvimetry, in addition to previ-

ously known genetic damage to the fetus, occasionally causes leukemia and other malignant disease in the unborn child.

J. Chassar Moir (Oxford), in Letter to the Editor, *Lancet 2*:99, July 14, 1956, condemns the use in pregnancy of the Thoms method of brim pelvimetry as a leukemogenic hazard to the infant. As an example of excessive roentgen diagnosis he refers to a patient with pulmonary tuberculosis who had 127 chest radiographs in five years. He recommends minimizing the amount of radiation used for individual exposures, and concludes: "If the recent publicity concerning the genetic hazards of radiation has done nothing else, it will have served a useful purpose by reminding clinicians of the potential dangers of the examinations which they sometimes so light-heartedly request."

H. S. Breton, in Correspondence, *Brit. M. J. 1*:1111, May 12, 1956, suggests repeated roentgen-ray examinations of the chest in mass screening for pulmonary tuberculosis as a possible trigger cocarcinogenic etiologic factor in lung cancer together with cigarette smoking, air pollutants, etc.

Peller and Pick, in Correspondence, *J. A. M. A. 147*:893, Oct. 27, 1951, reported that the incidence of leukemia among physicians is four times that among the general population, and eight to nine times higher among radiologists than among other physicians.

CURRENT BOOKS OF INTEREST

LUNG CANCER. By Seymour M. Farber, M.D., Associate Clinical Professor of Medicine, University of California Medical School, Lecturer in Diseases of the Chest, University of California School of Public Health. Springfield, Illinois. Charles C Thomas. 1954. 157 pp. $4.75.

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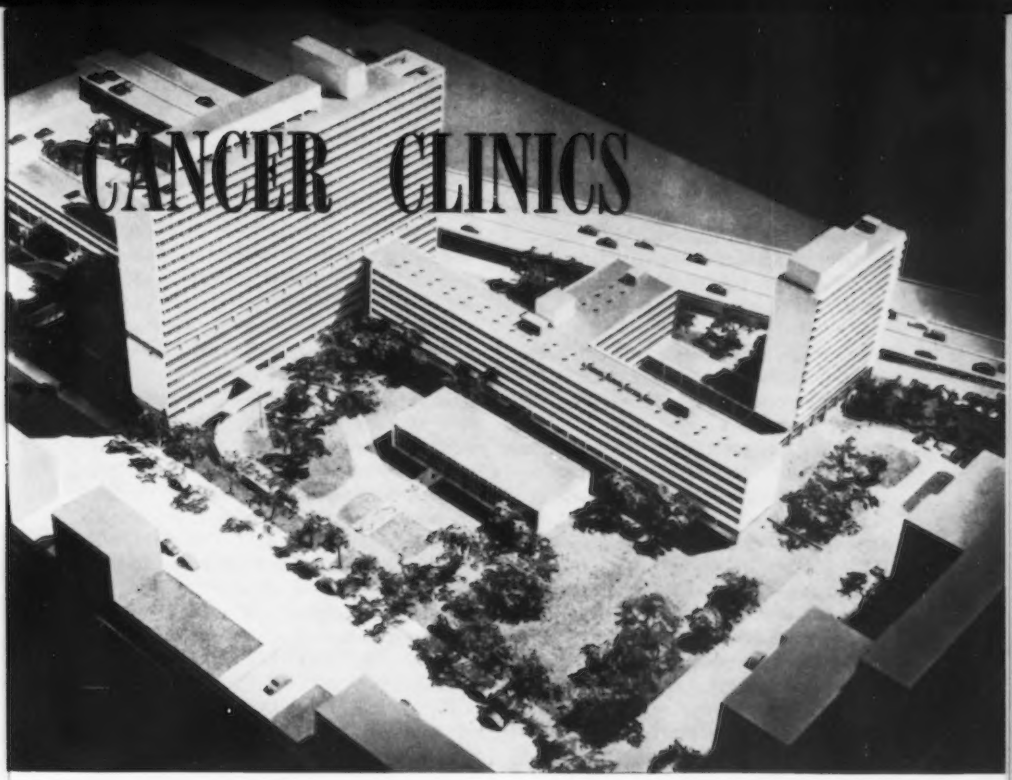

Occupational Cancer

with Special Reference to Carcinoma of the Lung in Chromate Workers

Marvin Kuschner, M.D. and Norton Nelson, Ph.D.

DR. KUSCHNER: The recognition and investigation of occupational tumors serve several important functions. First and foremost, of course, such studies are the basis for the elimination or protective modification of industrial procedures which are associated with a high cancer risk. To the extent that these are successful, morbidity and mortality from cancer are reduced. Secondly, a study of occupational tumors and of the specific agents that cause them has provided the tools for all of the current approaches to experimental carcinogenesis. Thirdly, the very fact that we have available to us what might be termed human experimental models in which such varied tumors as carcinoma of the skin, urinary bladder, and lung are produced by specific carcinogens has led to the justifiably optimistic concept that many human tumors are produced by other exogenous environmental carcinogens and are therefore potentially preventable.

The sequence of events in the investigation of occupational tumors has fol-

Synthesized from staff conferences and teaching conferences of the Departments of Pathology and Industrial Medicine, New York University-Bellevue Medical Center.

lowed a pattern which is now almost classic and which has been extended to environmental tumors in general. There is initially the recognition of an unusually high incidence of a particular tumor in a particular segment of the population. This is followed by the identification of a material or a variety of materials to which this population segment has been exposed. The specific agent or agents responsible for tumorigenesis have then been isolated by reproduction of the disease in experimental animals. Finally, once identified, the offending agents are eliminated or persons exposed are suitably protected.

The study of carcinoma of the lung in chromate workers has double significance at this time. Apart from the importance of protecting this small group of individuals from the disease, any information we accumulate in regard to the pathogenesis of lung cancer in general, a tumor which is responsible for an increasing number of cancer deaths, is invaluable.

Dr. Nelson will outline for you the development of our present state of knowledge with regard to the lung cancer problem in the chromate industry.

DR. NELSON: Hazards associated with chromate chemicals became apparent shortly after their manufacture began. Difficulties were reported as early as 1827 and irritations of skin and mucous membranes have since been well recognized. However, it was only comparatively recently that a lung cancer risk was suspected. In 1932 Lehman in Germany reported such an association, citing observations going back to 1912. Although repeated reports issued from Germany, it was not until 1948 that Machle and Gregorius, reporting on the incidence of lung cancer in the seven major plants in this country, found that the crude lung-cancer death rate was twenty-five times that of the normal rate.

The industry is a relatively small one; forty-two deaths from lung cancer being the basis for Machle's report. Still the increase was sufficiently decisive to be significant. Several confirmatory reports have subsequently appeared in this country and recently a follow-up study six years after an earlier equivocal study in British plants found a definite increase in lung cancer.

These findings have been restricted to plants producing chromate chemicals and have not been reported from groups otherwise engaged in chromium technology. The plants are generally small with several stages of the process often going on in the same area; moreover, workers generally have had contact with all operations in the plant over their working career. Consequently with the typically long latent period of cancer induction, cases with exposure limited to one material or process have not been available. Accordingly, epidemiological definition of the active chemical has not yet been achieved nor, in these circumstances, is it likely that it will be. Recourse must therefore be had to other means, for example animal experiment, to pinpoint the dangerous part of the process. Such identification is a requirement for fully effective control.

DR. KUSCHNER: We are at the stage then at which we recognize the existence of a high risk of lung cancer in the chromate-producing industry and we suspect a number of materials or types of materials of being responsible for this high incidence. In a sense we are at the same stage that Potts had arrived at with the recognition of the fact that chimney sweeps have a high incidence of scrotal cancer and that this was probably caused by the complex material known as soot to which they were exposed. To identify the specific hazardous material or materials and thereby take suitable precautions against exposure to them and to study the factors involved in the pathogenesis of such tumors would seem now to require the reproduction of the disease in experimental animals. This is a problem which is currently engaging our attention.

In attempting first to induce lung tumors in animals comparable to human bronchogenic carcinoma, we have exposed rats and mice to high concentrations of known potent polycyclic hydrocarbon carcinogens administered by aerosol inhalation and by direct intratracheal instillation. These techniques failed to produce tumors. It is not surprising then that at-

tempts to produce such tumors by the administration of chromium compounds by means of similar techniques would present difficulties, for it seems reasonable to assume that these compounds are probably not as potent as the hydrocarbons. These failures are not to be taken as evidence that the materials in question have no human significance. One problem that has constantly recurred in experimental reproduction of human environmental tumors has been the problem of adequate dosage. Thus skin tumors were not achieved with coal tar until prolonged and persistent painting was performed. Similarly the early failures to produce bladder tumors in rodents with aromatic amines might be considered a dosage problem since the significant carcinogen, a product of metabolic hydroxylation, did not reach the bladder in sufficient quantities in these species.

Using a modification of a technique devised by Andervont in which the lungs of animals are transfixed by threads containing a potential carcinogen and by impacting carcinogen-laden pellets in the bronchi of rats, we have been able to produce squamous-cell carcinoma of the lung in rodents. These have been produced by the same hydrocarbons that failed to produce tumors when given by inhalation or by intratracheal injection. It is our present feeling that prolonged and persistent dosage may be necessary for the induction of lung tumors in animals and this in a sense parallels our ideas of the long exposures necessary in humans. The threads and pellets provide higher levels of dose over longer periods of time than have been achieved with other techniques of application of material to the bronchial mucosa. Utilizing these techniques we are currently exposing rats and mice to selected pure chromium compounds as well as such plant products as roast, residue and plant dust. It is hoped that the induction of tumors in such an experiment may lead to the isolation of the stage or stages in the processing of chromium compounds which are hazardous.

The successful techniques for the induction of lung cancer in animals involve in addition to the dosage advantages already discussed, procedures which traumatize the bronchi. Control animals undergoing the same operative procedures but unexposed to carcinogens have developed squamous metaplasia of bronchial mucosa. It may well be that carcinogenesis in the lung is a two-stage process progressing through squamous metaplasia to carcinoma. Such experimental observations are of particular interest in view of the reported correlation between squamous metaplasia and the inhalation of a variety of suspected pulmonary carcinogens, including compounds of chromium. They suggest that agents of importance in the pathogenesis of lung tumors may be those capable of inducing squamous metaplasia, others capable of inducing carcinomatous change in an area of metaplasia, and still others perhaps which are capable of producing both metaplasia and carcinomatous change.

Air Pollution in Foggie Olde London

The first recorded use of coal in Great Britain was in 852. Four centuries later, in 1273, during the reign of Edward I, by act of parliament the burning of coal in the city of London was forbidden, and in 1306 a heating contractor was condemned to death and executed under this act. However, this tragic law was soon relaxed to be in force only when parliament was in session. Queen Elizabeth in the 16th century gave audience at Westminster to a delegation of London women complaining of the "dangerous usage of coalle."

DOCTORS' DILEMMAS

Q *A 37-year-old white male office worker complains of vague left lower chest pain, belching after meals, and moderate regurgitation, which have persisted for about three months. Chest roentgenograms are not unusual, but the gastrointestinal series shows a hiatus hernia. Other laboratory reports are within normal limits. Diet and medication have not relieved the symptoms. Should surgical management of the hiatus hernia be considered at this time?*

A The symptoms described might well be caused by this patient's hiatus hernia. They could, however, easily result from gastrointestinal pathology, in particular an annular lesion of the colon with low to moderate grade obstruction. Small lesions of the colon are notorious in producing the symptoms described. The hiatus hernia may have been present for many years. Before surgical treatment is undertaken, careful studies of the colon should be carried out.

Q *A couple whose first child died at age 4 of acute lymphatic leukemia have requested advice concerning the advisability of having another child which they both very much want.*

A The parents themselves must make the decision, but they may be informed that there is no known contraindication to their having another child. On the basis of evidence at hand, the chance of another child having leukemia would be extremely slight. No mention is made of any possible degree of consanguinity existing between the parents, but in such a case they can be advised that there is little convincing evidence that acute lymphatic leukemia in man is a hereditary disease.

Q *A 39-year-old white man has as his only complaint persistent enlargement of the nodes in the right cervical chain for the last eight weeks. There are no palpable enlarged nodes on the left and physical examination and chest roentgenogram reveal no significant abnormalities. I am concerned, however, that this asymmetrical node enlargement may represent evidence of an occult malignant process, although careful examination of the head and neck has failed to reveal such a process.*

A Asymmetrical enlargement of cervical lymph nodes in an adult is almost always associated with malignant disease. Most often it represents metastases from a primary lesion in the mouth or pharynx, though occasionally it may be due to metastases from a viscus below the level of the clavicle. These primary lesions are often very small and obscure and the metastases present as the first symptoms of the underlying disease. Careful, repeated examinations should be carried out in a search for the primary tumor. Although Hodgkin's disease and lymphosarcoma are generally thought to involve multiple nodal areas and cervical nodes, bilaterally, malignant lymphoma may be confined ini-

tially to one side. Much of the uncertainty in this case might be dispelled by a biopsy, removing an entire node rather than by wedge sectioning.

Q *A 54-year-old white male with a 2-month history of serous discharge from the right nipple and a "lump" in the subareolar region on the same side presents himself. Examination reveals a 3-cm. discoid, freely movable mass in the right breast. Gentle manipulation expresses one drop of greenish fluid from the nipple. Although the mass is movable over the chest wall, there is some question of fixation to the base of the nipple. There is no palpable lymphadenopathy. What management is indicated for this patient?*

A The history and physical findings could be consistent with either gynecomastia or cancer of the male breast. The importance of nipple discharge in cancer of the male breast has recently been pointed out. The mass should be excised for immediate histological examination and radical mastectomy should be performed if the pathologist's diagnosis is cancer. The survival rate parallels breast cancer in the female — approximately 75 per cent when the tumor is confined to the breast, with a sharp drop to approximately 30 per cent when the homolateral axillary lymph nodes are involved.

Q *I first saw a 52-year-old man three months ago. Except for fatigue and weakness his complaints were vague. Hemoglobin was 8 gm. Otherwise hematological and bone marrow studies were unremarkable. A complete gastrointestinal survey was unrevealing. After a transfusion the patient became asymptomatic, but in less than three weeks his hemoglobin had fallen from 15 back to 8 gms. Stool examinations now show persistent occult blood despite the patient's meat-free diet. Recent repeat gastrointestinal survey is again unremarkable. Is exploratory laparotomy indicated at this time?*

A Occult blood in the stool is a definite indication of bleeding from the gastrointestinal tract. While barium-enema examinations are often valuable in arriving at a diagnosis, a negative report from the roentgenologist may engender a false feeling of security. Existing neoplasms in the colon are not shown in approximately 5 per cent of barium enemas. If polyps are included, perhaps 15 per cent of existing lesions may be overlooked on roentgen-ray examination. The lesions most likely to be causing this patient's bleeding are polyps, tumors of the small intestine, small ulcerating carcinoma of the stomach, lipomas involving the gastrointestinal tract, or, more rarely, Meckel's diverticulum, chronic intussusception, or carcinoma of the ampulla.

Q *A 63-year-old woman had a radical mastectomy 19 years ago which was followed by roentgen-ray therapy. She remained well until eight months ago when the irradiated skin became ulcerated. The ulcer, approximately 1 cm. deep and 2 cm. in diameter, has not been treated and shows no sign of healing. What treatment is suggested?*

A It is important to establish the diagnosis without delay by miscroscopic examination of tissue from the margin of the ulcer. The specimen should include a portion of normal tissue. If the diagnosis, as is probable, is recurrent carcinoma, roentgen-ray therapy would be indicated. Much more rare is the possibility of benign necrosis due to radiation fibrosis with altered blood supply to the area. Such a negative biopsy should be repeated several times for confirmation. Wide excision and skin graft would then be the suggested treatment.

new developments in cancer

New Dimension . . .

Cell life, as recorded on 300,000 feet of movie film by Charles M. Pomerat of the University of Texas, will be shown to medical students everywhere. Filmed with phase-contrast microscopy under an American Cancer Society grant and supported further with an award of $30,000 from Abbott Laboratories, the pictures are offered to medical schools. The movies show that cell life is a ceaseless, surging series of activities, a constant groping in the environment for food, bitter battles with natural enemies, and triumph over age and death by constant growth and division. The offering brings a new day and a new dimension to medical education, replacing text-book representations that make the cell appear as dynamic as a doughnut.

Cancer Turns Back the Clock . . .

Involuntary aspects of thyroid cancer have been demonstrated by J. B. Trunnell and Paul Wade at M. D. Anderson Hospital, Houston. They first traced the process by which the thyroid develops in chick embryos and found that the embryonic gland produces ever-larger iodine-containing molecules. The developing gland followed this production schedule: 4 or 5 days—traps iodine; 8.3 days—makes monoiodotyrosine; 9.3 days—makes diiodotyrosine; 10 days—makes thyroxine. The same stepwise chemical process is followed by the adult gland in manufacturing thyroid hormone. But, the investigators found, some benign and malignant human thyroid tumors make little or no thyroxine—although they do produce mono- or diiodotyrosine. The scientists now are attempting to find the assembly-line fault in abnormal glands—to determine whether it lies in a substrate, an enzyme system, a gene, or an organizer.

4-APP Reduces Tumors . . .

A new preparation, 4-APP or 4-aminopyrazolo (3, 4-d) pyrimidine, has arrested the growth of some cancers both in culture and in experimental animals in tests at M. D. Anderson Hospital, Houston. Unfortunately, its toxic qualities are great. 4-APP was synthesized by Roland K. Robins and C. C. Cheng at Highlands University and tested in Houston by T. C. Hsu and Robert Fuerst. In tissue culture, the drug virtually destroyed all of a human cervical cancer, inflicting only minor damage on normal tissues. The growth of tumors transplanted to mice could be held at a virtual standstill so long as the animals were treated with 4-APP but, when the drug was withdrawn, tumor growth resumed.

New Book . . .

In his book, "*The Medical Care of the Aged and Chronically Ill*" (Little, Brown & Co.), Dr. Freddy Homburger of Tufts College Medical School vigorously attacks the defeatist attitude many doctors have toward their hopelessly ill and infirm patients. An excellent guide for the management of all common chronic conditions, the volume is particularly useful in counseling on advanced cancer.

"When the surgeons, the radiologists, the chemotherapists have all failed," Homburger states, "there remains a patient who is hopelessly ill yet still alive, and to make him comfortable requires all the skill and pharmacological knowledge the practitioner commands, with all the commiseration and compassion one human being can give another."

The book reviews briefly and brightly specific chemotherapeutic weapons and suggests that much can be done to support the patient through terminal phases of the disease. A few of the many recommendations follow:

Intra-arterial nitrogen mustard. Particularly in treating tumors of the face and pelvic region, nitrogen mustard administered through a polyethylene catheter into an artery leading to the lesion frequently has been helpful.

This is hospital, not office, procedure.

Bedside manner. The physician's attitude greatly influences the patient. "If an air of resignation pervades the atmosphere whenever the physician appears, this does not contribute toward making the patient feel better. If, on the other hand, false cheerfulness is displayed during professional visits, it will not fool the patient long. A balance must be found—something no textbook can provide and few fortunate practitioners discover instinctively."

Gloom chasers. Patients who had predinner cocktails and after-meal highballs before their illness should be encouraged to continue to drink—but not to excess. Liquor potentiates barbiturates against insomnia, improves appetite and gives patients a feeling they can still do things.

Morale boosters also include short walks, wheelchair rides, card playing, radio, television, and visits from friends.

Diet. Small doses of insulin subcutaneously 20-30 minutes before meals may increase appetite. Protein-anabolic androgens help keep patients in good nutritional condition when they are not contraindicated as in prostatic cancer. Emphasis should be on nonfilling foods with high energy content—with the patient's own culinary likes firmly in mind whenever possible. Vitamin supplements and protein concentrates usually should be given. The patient's digestive status and comfort must be considered.

Analgesics and narcotics. In pain-ridden terminal cases, analgesics and narcotics should be used to tolerance and within limits compatible with maintaining life. "There is nothing more ridiculous than to fear addiction in these patients, nothing more cruel than to substitute placebo injections because the physician (or sometimes the nurse) decides that the patient is an addict and does not really need medication." Paradoxically, it is sometimes desirable to combine narcotics such as morphine with stimulants such as cocaine. The cocaine counteracts the mental depression occasioned by morphine and produces a feeling of exhilaration. The use of cortisone with analgesics or narcotics is based on the same reasoning.

Neurosurgery. In relatively rare cases involving protracted and intensive pain (as in facial lesions and lesions compressing nerve roots), section of sensory nerves or roots or, in exceptional situations, prefrontal lobotomy frequently has more to offer than analgesia.

Rehabilitation. Patients cured but mutilated by surgery (as in mastectomy, laryngectomy, amputation, etc.) must be helped to readjust. "It is first of all necessary that the physician himself believe that the price for survival was worth the sacrifice. The physician must instill this feeling into his patients without much talk but rather by his confident attitude." He must also make every effort to obtain optimal function.

Dry Colostomy. "At its best, a colostomy is a cleaner and more convenient way for defecation than that provided by nature; at its worst, it is a serious infirmity." Colostomies should be well constructed and patients well instructed. Psychiatric complications can be minimized by intelligent medical management. Sympathy is no more indicated than it is for a person with normal bowel function.

Wet Colostomy. "At first sight, it seems an almost unacceptable degree of mutilation to remove rectum, uterus and bladder, leaving the patient with an abdominal cloaca which is constantly draining. However . . . this situation is nearly always accepted by these patients who were in extreme pain before operation, and they often adjust to the disability to a surprisingly satisfactory degree." If the physician regards wet colostomy as a dreadful calamity, this point of view may easily be passed on to the patient. If he feels that a colostomy is a modest price for redemption from death or suffering, his serene attitude may instill confidence into patients and help them to make the best of it.

Laryngectomy. Laryngectomized patients will make their best progress in regaining speech in organized speech training centers. About 80 per cent of these patients are capable of acquiring esophageal speech. Reed larynxes and other mechanical devices also help.

"*The Medical Care of the Aged and Chronically Ill*" is full of common sense and good medicine. It should be in the library of every physician.

Detecting Gastric Cancer . . .

Difficult-to-detect stomach cancer now is being found with good accuracy by cytological methods developed by Robert J. Bolt of the University of Michigan. The test, which takes twenty to thirty minutes of the patient's time and two hours of a technician's, goes like this: (1) the fasted patient swallows about 18 in. of a small stomach tube; (2) stomach contents are drawn off and spun and the sediment fixed, stained, and examined under the microscope; (3) about 500 cc. of alkaline solution containing chymotrypsin (which digests away the mucus) is introduced into the stomach; (4) the stomach content again is withdrawn and examined. Positive results so far have been about 100 per cent accurate, but negative results are not dependable. The test has been superior to those involving the use of brushes, balloons, or sponges.

References to Occupational and Environmental Cancer in Previous Issues of CA

2:97, May, 1952 Tobacco and lung cancer.

2:195, Nov., 1952 Industrial aspects of cancer of the skin.

2:199, Nov., 1952 Precancers of the skin; their recognition and management.

3:68, March, 1953 Complications following radiation therapy.

3:73, March, 1953 Influence of sunlight on skin carcinogenesis.

4:47, March, 1954 The place of tobacco in lung-cancer etiology.

4:49, March, 1954 The place of tobacco in the etiology of lung cancer.

5:88, May, 1955 Smoking and lung cancer: pros and cons.

5:95, May, 1955 Lung cancers and their causes.

6:156, Sept., 1956 Etiology of bronchogenic carcinoma.

6:169, Sept., 1956 Current status of lung-cancer research; some pathogenetic aspects.

proven); (2) induce formation of an isocarcinogen; or (3) accelerate the appearance of tissue "age changes."

Furth (Harvard) showed that, in mice at least, estrogen governs breast growth and function, not by its direct action on breast tissue, but rather by stimulating the growth of "mammotrope" cells of the pituitary. The cells produce a mammotropic hormone which enlarges breasts. He stimulated tumorous development of these cells by giving animals large and sustained doses of estrogen. Then he transplanted the pituitary (mammotropic) tumor to a variety of intact and aglandular male and female mice and found that, in suitable animals, massive mammary glands, full of milk, developed readily. This occurred in males as well as females. The more estrogen animals were given the larger became the mammotrope area of their pituitaries -- and the larger also their breasts. The observations indicated that hypophysectomy may aid some breast cancer patients by ridding them of mammotropic hormone sources; eventually, however, cancer cells not dependent upon hormone stimulation grow, and a relapse occurs.

Engel (Harvard) told how he had isolated human ovarian and adrenocortical tissues and showed, in vitro, that he could convert androgens into estrogens. This raised the question as to whether this same process occurs in women whose breast cancers become worse under androgen therapy.

Hormones -- Clinical. What is the value of hypophysectomy in breast cancer?

Luft and Olivecrona (Karolinska) reported on 52 cases, 41 of which could be evaluated. Of the 41, a total of 22 showed objective remission and 19 did not. Average remission was 17 months and the longest to date (and still in remission) is three years. All these were advanced and metastatic cancers; and some patients improved by hypophysectomy had relapsed following remissions from castration and adrenalectomy.

Lawrence, Tobias, Born and McCombs (U. of Calif.) reported giving up to 26,000 rad with a 340 million-volt proton beam to the pituitaries of 26 breast-cancer patients. While clinical evaluation of the treatment will have to await a larger series, it was found that hypophysectomy by this means was 95 per cent or more complete, iodine uptake by the thyroid and excretion of urinary gonadotropins were depressed markedly, damage to skin and other normal tissues was minimal, and some patients were helped. Patients were treated in six sessions (5-8 minutes each) over two weeks. While the

method is admittedly "not an answer to the breast cancer problem," five patients are still alive 13 to 19 months after irradiation. Objective arrest or regression lasted from one month to one year.

Cade (London) expressed enthusiasm for adrenalectomy in breast cancer. "No other treatment, with the exception of hypophysectomy, has given similar results." In the last four years 135 breast-cancer cases were submitted to bilateral adrenalectomy and oophorectomy. In about 30 per cent, there was a regression of skeletal, visceral and cutaneous lesions. Subjective improvement, including complete relief of pain and a return to a near normal life in formerly bedridden patients, was noted in 55 per cent. In this series, the effect of treatment could not be correlated with tumor histology, age of the patient or stage of disease. Thirty-five patients are alive from one month to three years after operation. Operative mortality has been seven of the 135 and three in the last 70 cases.

Pearson (Sloan-Kettering) reported that calcium excretion -- during the menstrual cycle, following oophorectomy and during estrogen and progesterone administration -- has led to the concept of two kinds of mammary cancer, estrogen-dependent and estrogen-independent. The excretion studies also have been useful, he said, in evaluating various types of treatment.

Hertz (NCI) said amphenone suppresses adrenal function but has limited use for "chemical adrenalectomy" because of its toxicity -- when the drug is withdrawn rebound effects include severe mental derangement and other symptoms of Cushing's syndrome. It could not be used long enough to determine its therapeutic value, if any, in breast cancer. It suppresses thyroid as well as adrenocortical function.

Kennedy (U. of Minn.) said that an orally administered halogenated male hormone (9α-fluoro-11-β-hydroxy-17-methyl-testosterone) gives generally about the same results in breast cancer as testosterone. Fourteen of twenty-nine patients treated with it showed objective regression of the tumor. In his dosages, side effects were slight.

The Society's annual national award went to Dr. Gioacchino Failla and Dr. Edith Quimby of the College of Physicians and Surgeons, Columbia University, for their work on radiation dosage.

(To be continued in next issue.)

Dr. George E. Pfahler—Friend of ACS and CA

As this issue of CA goes to press comes the news of the death from leukemia of Dr. George E. Pfahler on the 83rd anniversary of his birth. He was the oldest practicing radiologist. His work in this field began shortly after Roentgen's discovery and continued actively until the day before his death. He was always interested in cancer control and cooperated effectively with the American Cancer Society. In his last few days he selected from his slide collection, for use in a future issue of CA, an excellent group of skin-cancer illustrations, including one of his own hand mutilated by exposure through the early years to roentgen ray.

His hand and the leukemia that he fought successfully for so many years illustrate the possible dangers inherent in any new therapeutic modality and the necessity for prompt development of protective measures.

[*See also An Appreciation of Dr. Pfahler by Dr. James T. Case in CA—Bull. Cancer Progr. 5:11-13, Jan., 1955; and the guest editorial by Dr. Pfahler in the same issue.*]

COMING MEDICAL MEETINGS

Date 1957	Conference	City	Place
April 8-12	American College of Physicians	Boston, Mass.	Mechanics Hall
April 11-13	American Association of Pathologists and Bacteriologists	Washington, D. C.	
April 12-14	American Association for Cancer Research	Chicago	
April 14-20	American Society for Experimental Pathology	Chicago	
April 15-21	Pan-American Medical Association, Tenth Congress	Mexico City, D.F.	
April 25-29	Pan American Congress on Cancer Cytology	Miami Beach, Florida	Eden Roc Hotel
April 29-May 2	International Academy of Proctology	New York City	Plaza Hotel
May 5-8	Aero Medical Association	Denver, Col.	
May 5-10	International Congress of Otolaryngology	Washington, D. C.	Hotel Statler
May 12-13	International Congress of International Society of Bronchoesophagology	Philadelphia	
May 14-17	International Cancer Campaign Symposium on Biochemistry of Cancer	London	
May 15-17	American College of Cardiology	Washington, D. C.	Hotel Willard
May 19-24	National Conference of Social Work	Philadelphia, Pa.	
May 30-31	American Geriatrics Society	New York City	Waldorf-Astoria
May 30-June 1	American Radium Society 39th Annual Meeting	Quebec, P.Q.	Chateau Frontenac

Clinical Fellowships of the American Cancer Society

The American Cancer Society announces that its program of Clinical Fellowships will continue through the institutional year July 1, 1958-June 30, 1959 with Fellowships commencing July 1, 1958.

A limited number of Fellowships are offered to institutions whose postgraduate training programs are approved by the Council on Medical Education and Hospitals of the American Medical Association. These Fellowships offer graduates in medicine opportunities for postgraduate training, emphasizing diagnosis and treatment of cancer.

Applications from institutions for the year 1958-1959 must be submitted by Deans, Executive Officers, or Department Heads prior to April 15, 1957. Note change in deadline from previous years. Further information may be obtained from:

Director of Professional Education,
American Cancer Society, Inc.,
521 West 57th Street,
New York 19, N. Y.

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